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ERRATA

Please note the following corrections in the index, December 1954 issue:

p. 1276, column 1, line 36: Fistula, *uterovesical*, 374

p. 1280, column 2, line 14: Nourse, M. H. and Wishard, W. N. Jr. *Uterovesical* fistula with fetal parts presenting in external urethral meatus, 374

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A METHOD FOR ESTABLISHING PORTAL DRAINAGE OF ADRENAL VENOUS BLOOD IN DOGS WITH METABOLIC STUDIES INCLUDED

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From the James Buchanan Brady Urological Institute, the Johns Hopkins Hospital, Baltimore

It is well known that the liver is capable of reducing or altering the activity of many steroids. The ability of the normal liver to prevent the usual biologic activity of many androgens and estrogens passing first through the portal system is well established.[1-7] On the other hand, there is evidence that the primary physiological activity of some steroids persists despite primary circulation through the portal system. The oral activity of cortisone, cortical extract, corticosterone, and dehydrocorticosterone suggests that these substances fall into this category.[8-11] There is evidence that desoxycorticosterone acetate (DCA) may also be rendered only partially inactive by passage through the liver.[12-14] The demonstration by Eversole[15] and Butcher[16] that adrenals transplanted to

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* American Cancer Society Clinical Fellow at the time this work was carried out.

Note by editor. This manuscript was awarded a prize in the essay competition of 1951 sponsored annually by the American Urological Association under the Committee on Scientific Research, Dr. Miley B. Wesson, chairman.

† Present Address: Vanderbilt University Hospital, Nashville, Tenn.

[1] Burrill, M. W. and Greene, R. R.: The liver and endogenous androgens. Proc. Soc. Exper. Biol. and Med., **44:** 273, 1940.

[2] Burrill, M. W. and Greene, R. R.: Effect of rats' liver on activity of testosterone and methyl testosterone. Endocrinol., **31:** 73, 1942.

[3] Biskind, G. R. and Mark, J.: The inactivation of testosterone propionate and estrone in rats. Bull. Johns Hopkins Hosp., **65:** 212, 1939.

[4] Grayhack, J. T. and Scott, W. W.: Observation of the *in vivo* inactivation of testosterone propionate by the liver of the white rat. Endocrinol., **48:** 453, 1951.

[5] Drill, V. A. and Pfeiffer, C. A.: Effect of vit. B complex deficiency controlled inanition [illegible] strogen by the liver. Endocrinol., **38:** 300, 1946.

[illegible] E. L.: Inactivation of estrogenic hormone of the ovary [illegible] l and Med., **39:** 361, 1938.

[illegible], J. W.: The effect of inanition on inactivation of estrogen by the liver. Endocrinol., **43:** 78, 1948.

[8] Bowland, E. W. and Headley, N. E.: Oral use of cortisone acetate. J.A.M.A., **145:** 8, 1951.

[9] Conn, J. W. and Silverman, F. W.: Effect of orally administered cortical extract upon sodium and chloride balance in Addison's disease. J. Clin. Invest., **18:** 488, 1939.

[10] Kuizenga, M. H., Nelson, J. W. and Cartland, G. F.: Comparative parenteral and oral assays of adrenal cortical hormone substances. Am. J. Physiol., **130:** 298, 1940.

[11] Thorn, G. W., Emerson, Kendall, Jr., and Eisenberg, Harry: Oral therapy in adrenal insufficiency. Endocrinol., **28:** 403, 1938.

[12] Mark, J.: Inactivation of desoxycorticosterone acetate. Endocrinol., **31:** 582, 1942.

[13] Eversole, W. J. and Gaunt, R.: Desoxycorticosterone: A. Its loss in digestive tract; B. Effect on water intoxication. Proc. Am. J. Physiol. Soc., **133:** 271, 1941.

[14] Grollman, Arthur: The comparative activity of desoxycorticosterone and other crystalline derivatives and of purified extracts of the adrenal cortex. J. Pharm. and Exper. Therapeutics, **67:** 257, 1939.

[15] Eversole, W. J., Edelman, Abraham and Gaunt, Robert: Effect of adrenal cortical transplants on life maintenance and "water intoxication." Anat. Rec., **76:** 271, 1940.

[16] Butcher, Earl O.: Adrenal autotransplantation with hepatic portal drainage in the rat. Endocrinol., **43:** 30, 1948.

the mesentery or the spleen of rats maintain life, supplies further evidence that the adrenal cortical steroids necessary for life, continue to function despite a primary hepatic circulation.

Adrenal androgens have been implicated in the changes characteristic of the adrenogenital syndrome.[17] It has been suggested that they may also be responsible for stimulating the growth of carcinoma of the prostate following the removal of the testes. In an attempt to eliminate these androgens, bilateral adrenalectomy has been performed in the treatment of adrenal hyperplasia[18] and is at present being used by some as one step in the treatment of advanced carcinoma of the prostate.[19, 20]

It seemed possible that if adrenal androgen were similar to testicular androgen,[1] testosterone,[2] or testosterone propionate,[3] primary passage of adrenal blood through the portal circulation might eliminate adrenal androgenic substances. Furthermore, it seemed probable that under these circumstances the adrenal substances necessary to life would continue to function physiologically.

With this in mind, an attempt was made to create a situation in which the venous blood of the adrenal would pass through the portal circulation prior to entry into the systemic circulation. The following is a report of the results obtained in this attempt.

MATERIALS AND METHODS

Adult male dogs were used in all experiments. Intravenous sodium pentobarbital was used as the anesthetic agent.

Surgical Procedures

Adrenalectomy. Two dogs were subjected first to left adrenalectomy and 2 weeks later to right adrenalectomy. These animals serving as controls were studied in the same manner as the others to be described.

Adrenal implants. Despite previously reported unsuccessful attempts to obtain life-sustaining glandular tissue with free grafts of adrenal in the dog,[21, 22] we undertook autogeneous transplantation of adrenal tissue to the spleen in four dogs and to the subcutaneous tissue in two. In four dogs, the left adrenal was removed, divided into four or five small portions, and implanted in the spleen in three animals and in the subcutaneous tissue in the other. The contralateral adrenal was subsequently removed. In the remaining two animals, unilateral adrenalectomy was performed initially. The removal and implantation of the remaining adrenal was done at a later date. The dogs were then maintained with injections of percorten* and the adrenal extract, eschatin† for as long as 17 days. With cessation of replacement therapy, all the animals in this group died of adrenal insufficiency. These failures led us to a consideration of methods for creating a portal venous drainage for the relatively intact adrenal.

---

[17] Wilkins, Lawson: The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence. Springfield, Ill.: Charles C. Thomas, 1950, p. 260.

[18] Lewis, R. A., Klein, R. and Wilkins, L.: Congenital adrenal hyperplasia with pseudohermaphroditism and symptoms of Addison's disease: Clinical course following bilateral total adrenalectomy, with metabolic studies, pathologic findings and discussion of etiology. J. Clin. Endocrinol., **10:** 703, 1950.

[19] Huggins, C. and Scott, W. W.: Bilateral adrenalectomy in prostatic cancer; clinical features and urinary excretion of 17-ketosteroids and estrogen. Ann. Surg., **122:** 1031, 1945.

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[21] Crowe, S. J. and Wislocki, George B.: Experimental observations of the suprarenal glands with special reference to the function of their interrenal portions. Bull. Johns Hopkins Hosp., **25:** 287, 1914.

[22] Blodinger, I., Klebanoff, H. E. and Laurens, Henry: Suprarenal transplantation in the dog. Am. J. Physiol., **76:** 151, 1926.

Vascular shunts. Dragstedt[23] reported a method for shunting the adrenal venous blood flow to the portal circulation. This relied on the creation of an Eck fistula with ligation of the vena cava above the site of the portal vein-caval anastomosis as well as below the renal veins. From a practical standpoint, ligation of the vena cava above and below the site of the renal veins seemed undesirable. An attempt was made to devise a procedure which would involve the use of the venous drainage from one kidney only. In attempting transplantation of the adrenals, Dragstedt as well as Levy and Blalock[24] had concluded that the blood vessels of the adrenal itself were too small for direct anastomosis to other vessels. However, the latter investigators demonstrated that the left renal pedicle could successfully serve as a pedicle for an autogenous adrenal gland graft in the absence of any other blood supply. In the procedure described by them, the left adrenal gland is completely freed of all blood supply except that arising from the renal vessels. Under these circumstances, the *en bloc* removal of the left kidney and adrenal with subsequent successful anastomosis of the renal vessels to the carotid artery and jugular vein will result in a viable functioning adrenal gland capable of sustaining life. Complete severence of all vascular connections of the adrenal gland except those going to or coming from the renal pedicle, seemed to offer a method of directing the adrenal blood to the renal vein, a vessel which because of its size and blood flow was suitable for anastomosis. For our purposes, following isolation of the adrenal in this way, the renal vein carrying the adrenal blood could be made part of the portal system by anastomosing it to the splenic vein. Because of its length and availability, the splenic vein seemed ideal as the portal end of the anastomosis. The technique used in performing this procedure was as follows (fig. 1):

A left subcostal incision was made. Upon entering the abdomen, the posterior peritoneum was incised and the left renal vein exposed. The spermatic vein was clamped, divided, and ligated. The renal vein was then skeletonized from the vena cava to the first obvious venules coursing from the adrenal toward the renal vein. Usually one to one and a half centimeters of renal vein could safely be isolated without impairing the adrenal connections. The next step involved dissection of the splenic vein from the pancreas. After an adequate length of this vessel was obtained, splenectomy was performed. A bulldog clamp was placed distally on the splenic vein. The upper pole of the adrenal was then freed, care

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* Brand of desoxycorticosterone acetate (DCA) U.S.P., Ciba Pharmaceutical Products, Inc.

† Extract of adrenal cortex of Parke, Davis & Co.

[23] Dragstedt, L. R.: The effect of diverting the adrenal vein blood into the portal vein on the blood sugar of dogs. Am. J. Physiol., **108**: 42, 1934.

[24] Levy, S. E. and Blalock, A.: A method for transplanting the adrenal gland of the dog with re-establishment of its blood supply. Ann. Surg., **109**: 84, 1939.

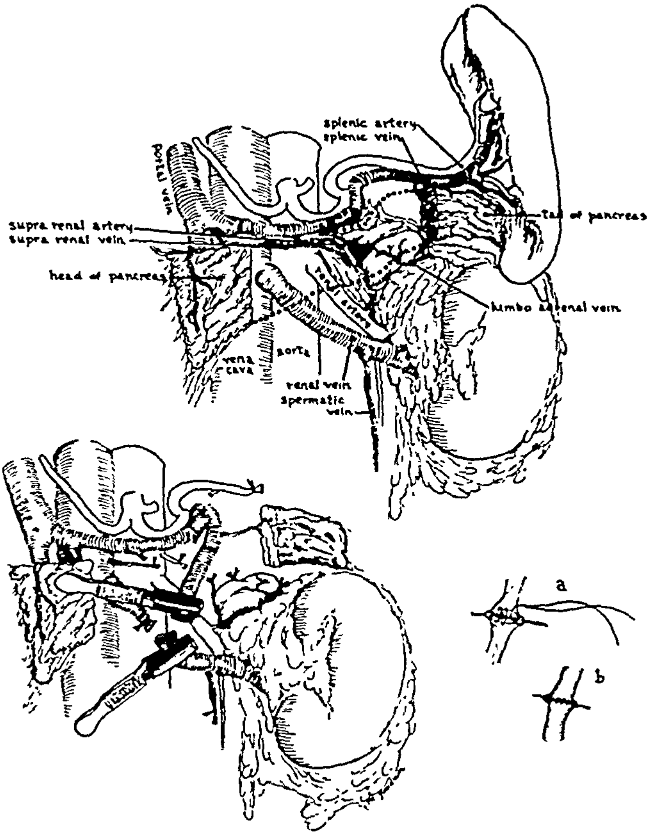

FIG. 1. Schematic drawing of pre- and postoperative views of renal-splenic anastomosis illustrating dependence of adrenal on renal pedicle for its blood supply. Insets *a* and *b* show vascular anastomosis.

being taken to divide and ligate all vessels. Next, the lumbo-adrenal vein was clamped, divided and ligated proximal and distal to the adrenal. All connections between the adrenal and the renal pedicle were meticulously preserved. The end result was an adrenal which moved freely on the superior surface of the renal pedicle but was held in close continuity with the renal hilum by fat and small vessels. At this stage, a bulldog clamp was placed proximally on the renal vein. The distal end was ligated; the vein was divided between this ligature and the bulldog clamp. The renal and splenic veins were approximated. Two stay sutures were used to join the vessels; an anterior and posterior continuous suture of 6-0 black silk, joining the stays, secured the anastomosis. Frequently, the splenic vessel was smaller than the renal, and this was compensated for, in part, in placing the sutures. The performance of this type of procedure seemed likely to result in portal drainage of adrenal venous blood through the newly created renal splenic anastomosis.

Twelve of the dogs on which this procedure was performed survived the operation. One to two weeks postoperatively, neo-iopax* was injected intravenously in anesthetized, dehydrated dogs in an attempt to demonstrate renal function on the operated side. It was felt that evidence of renal function on pyelography would probably be indicative of a patent venous anastomosis. Regardless of the functional status of the left kidney, a right adrenalectomy was performed three to six weeks after the shunt. Each of the dogs was supported with DCA and eschatin for one to seven days after the procedure.

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* Schering's brand of sodium iodomethamate.

Physiological Procedures

The three types of surgically prepared animals (adrenalectomized, adrenal implants, vascular shunt) were then studied and compared as to the adequacy of their adrenal function. Glucose tolerance tests, serum sodium and potassium determinations, and determinations of urinary 17-ketosteroid excretion were performed before and after each operation.

Glucose tolerance. Intravenous glucose tolerance tests were performed as described by Thorn.[25] A 20 per cent solution of glucose was given intravenously so that over a period of 30 minutes the unanesthetized animal received ½ gm. of glucose per kilogram of body weight. This made the absorption rate physiologically similar to the usual gastric absorption. A fasting specimen of venous blood was obtained as well as eight half-hourly post-infusion specimens. Glucose determinations, using the Folin-Wu[26] method, were run in duplicate. In most cases, glucose tolerance curves were determined before and after each operation.

Serum sodium and potassium. Serum sodium and potassium levels were obtained using the Perkin-Elmer[27] flame photometer. In most cases, at least three levels for each electrolyte were obtained before and after the various operative procedures.

17-Ketosteroids. Periodic 48-hour urine specimens were obtained on all dogs. Two or three such collections were made before and after the surgical procedures. On each of the specimens, 17-ketosteroid determinations were run using a modification of the Callow and Callow[28] method.

RESULTS (TABLE 1)

Adrenalectomy

In the two dogs in which bilateral adrenalectomy was performed our results agree with those previously reported.[21, 29] On the day the second adrenal was removed each of these dogs received a single injection of DCA and eschatin. One dog died three days after the procedure; the other animal survived for seven days. Figure 2 shows the results of the glucose tolerances, serum sodium and potassium determinations, and urinary 17-ketosteroids in one of these animals (dog 26).

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TABLE 1

Procedure	No. Animals	Result	
		Alive	Dead
Adrenalectomy, bilateral	2	0	2
Adrenal Implants	6		
(a) Splenic	4	0	4
(b) Subcutaneous	2	0	2
Attempted Shunts	12		
(a) Non-functioning IVP	3	0	3
(b) ?-functioning IVP	2	0	2*
(c) Definite function	7	5	2†

* Dog #22—Autopsy showed pneumonitis, left adrenal intact.
† Dog #29—Died from blood loss at time of right adrenalectomy, left adrenal intact.

Implants

All the dogs in this group died whether the implanted adrenal was placed intrasplenically or subcutaneously. Four dogs with splenic implants were given supportive therapy for from one to seventeen days following removal of all except the implanted adrenal tissue. The longest survival period after cessation of replacement therapy was 13 days.

One of two dogs with a subcutaneous implant survived 7 days after cessation of supportive therapy extending over a thirteen day period. The other lived only five days. The results of the studies of this dog are shown in figure 3 (dog 25).

Attempted Shunt

For consideration, we should like to divide the animals in this category into sub-groups based on the results of the pyelographic studies.

1) *Nonfunctioning left kidney on excretory urography.* In 3 dogs the urogram showed no evidence of renal function on the side of the attempted shunt. All three died shortly after removal of the right adrenal. A short description of the course of each of these dogs follows:

Dog No. 7, a 15.5 kg. male, failed to show left renal function on excretory urography performed 3 weeks after the attempted anastomosis of the left renal and the splenic veins. Forty-one days after the first operation, the right adrenal was removed. Supportive therapy was given for 4 days. Three days later the animal died. Autopsy revealed a small contracted left kidney and a normal right kidney. Grossly, there was no adrenal tissue present. The renal-splenic vein anastomosis was not patent.

Dog No. 11, an 11.6 kg. male, showed no left renal function on excretory urography performed 3 weeks after attempted shunt. Fifty-four days following the initial procedure, right adrenalectomy was performed. The animal was given DCA and eschatin for 6 days. A glucose tolerance test was performed on the fourteenth postoperative day. This showed a typical terminal hypoglycemic phase during which the dog became semi-stuporous. He died 48 hours later from adrenal insufficiency. Autopsy revealed a small atrophic left kidney. The renal

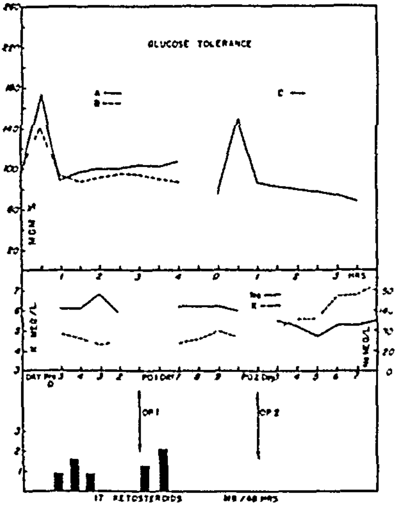

Fig 2 Dog No 26 Glucose tolerance A, preoperative B, post left adrenalectomy C, post right adrenalectomy OP 1, left adrenalectomy OP 2, right adrenalectomy

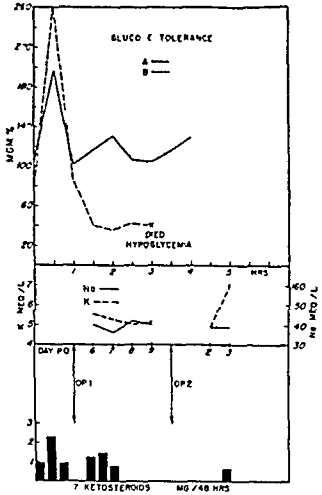

Fig 3 Dog No 25 Glucose tolerance A, preoperative B, post subcutaneous implantation C, post right adrenalectomy OP 1, subcutaneous implantation OP 2, right adrenalectomy

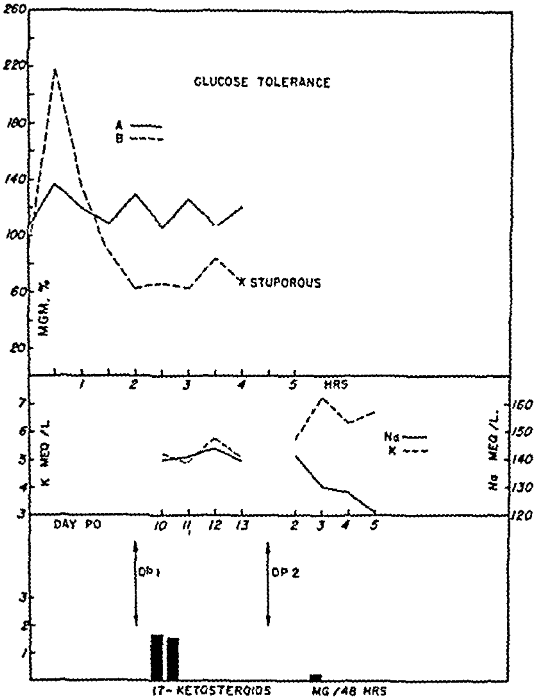

FIG. 4. Dog. No. 23. Glucose tolerance. *A*, post shunt. *B*, post right adrenalectomy. *OP. 1*, renal-splenic anastomosis. *OP. 2*, right adrenalectomy.

artery was patent. There were minute amounts of yellowish tissue resembling adrenal cortex present on the left. Microscopic sections of this tissue failed to demonstrate any adrenal cortical cells.

Dog No. 23 was a 17.6 kg. male. In this animal the left renal and splenic veins were purposefully ligated after the adrenal had been completely mobilized. Eighteen days later the right adrenal was removed. Eschatin and DCA were given for one day. Three days after operation, he became so lethargic that death seemed imminent. An intravenous glucose tolerance test was performed following which the animal died in a severe hypoglycemic crisis. Figure 4 represents the studies done on this animal. Autopsy revealed a firm left kidney, only slightly smaller than the right. The renal artery was patent throughout. At the upper pole of the left kidney there was a small, apparently intact adrenal gland. Grossly, the gland seemed to consist of a prominent congested medulla surrounded by a small rim of cortical tissue. Microscopic sections revealed complete disorganization of the adrenal cortex. The few remaining cortical cells were completely abnormal.

Questionable function on excretory urography. There was equivocal evidence of function in the operated kidney on excretory urography in 2 dogs. In one of these, a postoperative abscess at the upper pole of the left kidney had been drained. Seven days after removal of the right adrenal, the dog (No. 9) died in moderate hypoglycemia during a glucose tolerance test. Autopsy showed the left kidney to be almost the same size as the right, although badly scarred. The anastomosis was not functioning; there was no visible adrenal tissue present.

The other dog (No. 22) died within twelve hours of right adrenalectomy. Autopsy disclosed the presence of a diffuse patchy pneumonitis. There was an organized thrombus at the site of anastomosis. The left kidney was approximately normal in size. The ureteral vein was found to be 3–4 times larger than normal. The adrenal gland was grossly normal. However, on histologic study, it was seen that there was an area of infarction. The remainder of the gland was grossly abnormal. Dilated venous channels were everywhere in evidence. Atrophied and scarred tissue seemed to constitute almost the entire mass of the gland.

Definite function on excretory urography. There were seven dogs which showed unequivocal left renal function on excretory urography. Five of these survived contralateral adrenalectomy. One died in typical adrenal insufficiency, the other from blood loss. Each of these animals will be described briefly.

Dog No. 8, a 15.5 kg. male, showed bilateral renal function on excretory urography performed 3 weeks after the shunting operation. Forty days later, the right adrenal was removed. The dog received supportive therapy for 5 days. He has remained in excellent condition for over three years despite exploration of the left kidney and adrenal some 124 days after right adrenalectomy. At the time of this exploration, an apparently normal adrenal was visualized lying between the kidney and an apparently normal renal vein. The kidney and adrenal were completely mobilized. Only the small veins joining the kidney and adrenal gland were preserved. Two large ureteral veins were clamped, divided, and ligated. Despite the apparent interruption of all collateral circulation, this dog was able to withstand a glucose tolerance test performed within one week following this

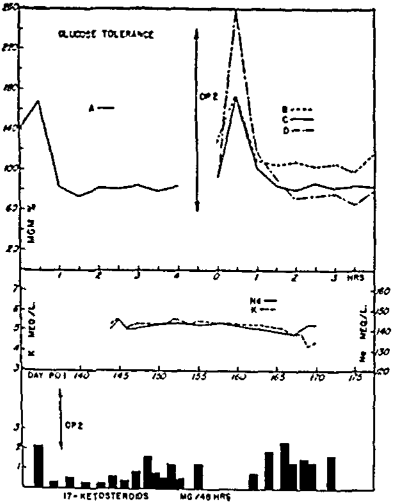

FIG. 5. Dog No. 8. Glucose tolerance. *A*, post shunt. *B*, post right adrenalectomy. *C*, post daily doses 40 mg. ACTH. *D*, post interruption of collaterals. *OP. 2*, right adrenalectomy.

procedure. On one occasion 40 mg. of adrenocorticotrophin were given daily for 6 days. No appreciable effect on the glucose tolerance test or the serum sodium and potassium levels was noted. Studies on this animal are shown in figure 5.

Dog No. 13, a 17 kg. adult male, showed good bilateral renal function on excretory urography (fig. 6) performed 3 weeks after the shunting operation. Thirty-two days later, the right adrenal was removed. Despite the demonstration of a slight but definite hypoglycemic tendency during the glucose tolerance test, the animal remained in good health. Serum sodium and potassium levels were normal. Fifty days after the shunt, an exploratory laparotomy was performed and an attempt was made to locate the splenic vein near the head of the pancreas. The vein which was thought to represent this vessel was isolated, ligated and divided. Following this, the serum potassium rose to as high as 6 mEq/L; however, the dog survived the glucose tolerance test. One week following this operative procedure, the left kidney was again exposed. A dilated ureteral vein was noted along with a few enlarged renal capsular vessels. The kidney appeared normal; a normal appearing adrenal was visualized adhering closely to the renal vein. The latter was isolated and divided near the hilum of the kidney. A brisk flow of venous blood was noted. The vein was clamped and ligated. Following this procedure, the dog was again able to survive despite a slight hypoglycemia during the glucose tolerance test. The animal died some 2½ years later during the induction of anesthesia administered to allow visualization of the vocal cords. At autopsy it was difficult to reconstruct the previous surgery. The kidney was grossly normal; there was a dilated ureteral vein. The renal

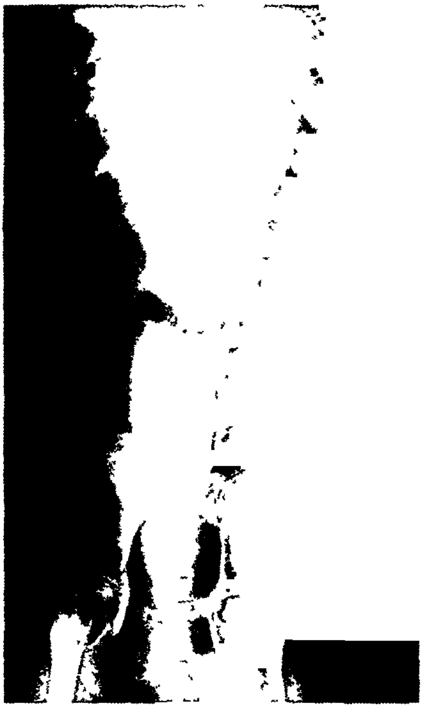

FIG. 6. Dog No. 13. Excretory urogram demonstrating postoperative function of left kidney.

artery was patent. Much to our surprise, the renal vein also seemed paten drained into a vein which lay on the inferior border of the pancreas and ent the superior mesenteric. There was a mass of scar tissue closely adherent t renal vein near the hilum of the kidney. The adrenal was found in this scar ti It was much smaller than a normal gland. The sites of anastomosis and lig of veins could not be made out. There were several small veins present in the region of the renal hilum; definite determination of the origin and termination of these was difficult. No venous connections to the small remaining adrenal tissue could be made out. Histologically, although the tissue was unmistakenly of adrenal origin, the cells appeared abnormal; there was atrophy of the zona glomerulosa.

Dog No. 14 was an adult male weighing 18.9 kg. at the time left renal-splenic vein anastomosis was carried out. Following this, excellent bilateral renal function was demonstrated on excretory urography. Forty-four days after the first operation, the right adrenal was removed. This dog has had essentially normal studies. He has remained in good health for over three years.

Dog No. 20 was an adult male weighing 20.4 kg. at the time of anastomosis. An excretory urogram 3 weeks later showed good renal function bilaterally. Thirty days after the original procedure, a right adrenalectomy was performed. The animal was supported for 4 days. Seventeen days after the removal of the right adrenal, the left kidney was exposed. It appeared normal. The ureteral veins again appeared enlarged. The adrenal appeared grossly normal. The renal vein was isolated near the hilum of the kidney and divided; a brisk blood flow was noted. The vein was then clamped and ligated. The splenic vein was ligated and divided distal to the anastomosis Despite this procedure, this animal has remained in good health for more than three years. The results of his studies are shown in figure 7.

Dog No. 21 was an elderly male weighing 23.6 kg. at the time of left renal-splenic vein anastomosis. A postoperative pyelogram revealed good bilateral renal function Twenty-five days after the initial operation, the right adrenal was removed. The dog was given DCA and eschatin for 4 days following this Within six days after cessation of supportive treatment, the animal died in typical adrenal insufficiency. At autopsy the left kidney was grossly normal. The venous anastomosis was patent. No adrenal tissue was found. Graphic representation of the studies in this animal is shown in figure 8.

Dog No. 28 weighed 16.3 kg. at the time the left renal-splenic vein anastomosis was performed. Excretory urograms demonstrated bilateral renal function. Two months after the original procedure, a right adrenalectomy was performed. An injury to the vena cava at its junction with the lumbo-adrenal vein resulted in sufficient blood loss to result in death from shock. At autopsy, the left kidney was normal The venous anastomosis was patent. The left adrenal seemed slightly decreased in size but was otherwise normal. Unfortunately the specimen was misplaced and microscopic sections are not available for histologic study.

Dog No 29 underwent a left renal-splenic anastomosis 37 days prior to right adrenalectomy. Unquestionable bilateral renal function was demonstrated on

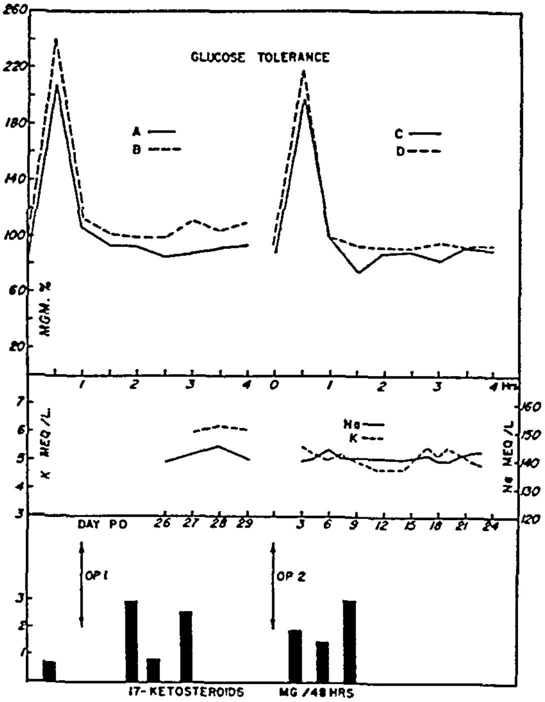

FIG. 7. Dog No. 20 Glucose tolerance. *A*, preoperative. *B*, post shunt. *C*, post right adrenalectomy. *D*, post ligation of splenic and renal veins. *OP. 1*, shunt. *OP. 2*, right adrenalectomy.

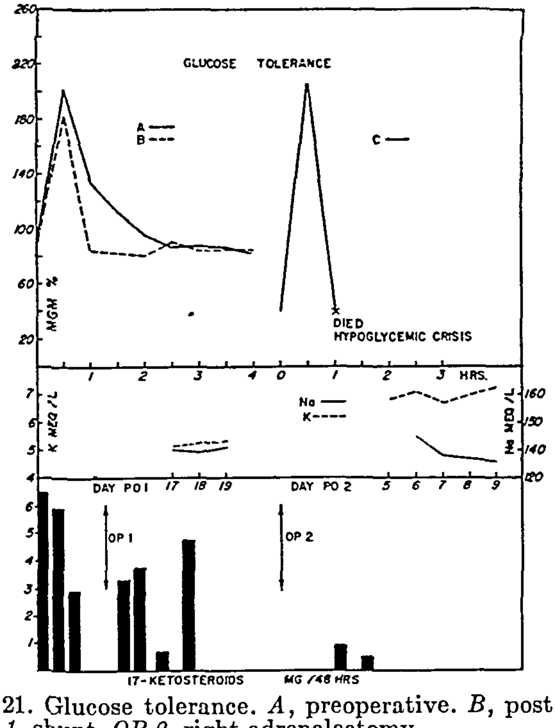

FIG. 8. Dog No. 21. Glucose tolerance. *A*, preoperative. *B*, post shunt. *C*, post right adrenalectomy. *OP. 1*, shunt. *OP 2*, right adrenalectomy.

excretory urography. Postoperative studies were essentially normal. The dog remains in apparent good health, some three years since adrenalectomy.

DISCUSSION

The failure of untreated dogs to live following bilateral adrenalectomy is in agreement with previous studies.[21-29] The inability of free grafts of adrenal tissue to support life in dogs is also established. This is not true of the rat[16] or the guinea pig,[30] but in the dog, despite evidence of some viable cortical tissue at the site of adrenal grafting, adequate functional adrenal has not resulted from implantation of the excised adrenal in the muscle, kidney, or omentum.[21-29] The survival and relatively normal state of dogs following unilateral adrenalectomy have been demonstrated previously.[21-29] Removal of one adrenal had no persistent effect on the glucose tolerance test or serum sodium and potassium levels.

The dogs in which anastomosis of the left renal and splenic veins was performed are of considerable interest. The purpose of performing this surgical maneuver was to attempt to divert the adrenal venous blood flow from the systemic to the portal circulation. The previous work of Levy and Blalock suggested that *en bloc* mobilization of the left kidney and adrenal would result in a diversion of the adrenal venous blood flow to the main venous drainage system of the kidney. Under these circumstances, continued adequate venous drainage of the adrenal would be dependent on the patency of the renal vein. One would expect failure of the renal-splenic vein anastomosis to result in marked impairment of the adrenal function if this were actually a critical pathway for adrenal venous blood flow. From our observations, this seems to be the case. None of the 5 dogs without definite postoperative bilateral renal function on excretory urography survived the removal of the contralateral adrenal. Four of these animals died in a fashion typical of adrenal insufficiency. Although each animal did not show all the manifestations of the syndrome, enough data were usually present to establish the diagnosis. In dog No. 23 the encapsulated congested adrenal on histologic examination was found to be completely disorganized. In the face of a nonfunctioning renal splenic vein anastomosis, he was unable to survive. The fifth dog in this group (No. 22) died within 12 hours after operation, there were definite patchy infiltrates throughout the lungs. Despite the thrombosis present at the anastomotic site, a grossly normal adrenal gland was present on the left. However, histologically the gland showed evidence of marked venous stasis with secondary atrophy and scarring. It was everywhere strikingly abnormal. In view of the type of replacement therapy employed, the stress of the pulmonary infection may have created a relative adrenal insufficiency. We have no definite evidence that such was the case. The functional status of the left adrenal in this particular instance is in doubt.

The survival of the dogs with definite postoperative bilateral renal function is in direct contrast to the failure of survival in the absence of definite evidence of renal function. Five of the seven animals in the former category survived at least two and a half years following right adrenalectomy. One of the dogs (No. 28) died from blood loss at the time of right adrenalectomy. He had a left adrenal which although slightly decreased in size appeared grossly normal. The venous anastomosis was patent. The other dog (No. 21) had no evident surviving adrenal tissue despite a normal kidney with a patent renal artery and vein. It seems probable that the failure of this adrenal to survive was due to interference with its arterial supply. In the situation created by the operative procedure described, the branches of the renal artery and vein passing to the adrenal constitute a pedicle for that organ. Interference with either the arterial supply to or the venous drainage from the gland is likely to result in a functionally inadequate adrenal.

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[30] Jaffee, H. L. On the transplantation of the guinea pig suprarenal and the functioning of the grafts. J. Exper. Med., 45: 587, 1927.

The demonstration that patency of the renal-splenic vein anastomosis is so vitally important to the achievement of satisfactory adrenal function suggests that under the condition created by the operative procedure described, this is the main pathway for the venous blood of the remaining adrenal gland. With the passage of time, a collateral venous circulation apparently develops which is capable of maintaining the adrenal in a functioning state despite interruption of the renal-splenic vein pathway (dogs Nos. 13 and 20). This statement presumes the success of the surgical attempts to interrupt this pathway. From observation at the time of exploration of the renal-adrenal area following the shunting procedure, it seems that the ureteral veins constitute the primary alternate pathway for renal and adrenal venous blood. Although we cannot state definitely that such is the case, it does not seem likely that an appreciable amount of the adrenal venous blood flow normally courses this pathway.

The adequacy of the life sustaining functions of the transplanted adrenals in the group of dogs with functioning anastomoses seems certain. This is evidenced by the following observations: 1) the fact that the serum sodium and potassium determinations were usually within normal range, although the latter occasionally strayed to the high side of normal; 2) the ability of these dogs to withstand the stress of a glucose tolerance test, although some of them showed a hypoglycemic tendency; and 3) the prolonged survival of these animals in apparently good condition.

It has been pointed out that not only do animals suffering from adrenal insufficiency develop hypoglycemia but they show a marked inability to tolerate even moderate degrees of this state. Our studies on dogs with nonfunctioning anastomoses have borne this out. In every instance in which a glucose tolerance was performed in these animals, the dog either died during the tolerance or became semi-stuporous and died within a day or two of it. Dogs with functioning anastomoses have survived the glucose tolerance test without serious difficulty. We cannot state with absolute certainty that the portal drainage is the only venous pathway available for adrenal venous blood under these circumstances and that it is the adrenal secretions being metabolized in or passing through the liver which account for this ability to withstand this stress in all the dogs with functioning renal-splenic vein anastomoses. However, the result obtained in dog No. 8 in which all veins in the vicinity of the adrenal except those going to the kidney or the renal-splenic channel were interrupted is good evidence that an animal subjected to the shunting procedure will survive the glucose tolerance test even if extraportal adrenal venous drainage is nonexistent.

The 17-ketosteroids performed failed to disclose any consistent observation other than the fact that the values seem to drop in animals in which the adrenals were totally absent. Values for most of the dogs were in such a low range that any attempt at a more detailed interpretation of the results seems hazardous.

We have gathered no evidence to support the idea that adrenal androgen will be eliminated by the passage of adrenal blood through the portal circulation. In 1941, Burrill and Greene[31] suggested that the liver failed to inactivate adrenal androgens. They based this suggestion on the observation that the rate of atrophy of the prostate of the 26-day old rat was not so great in castrate rats with adrenals transplanted to the posterior surface of the stomach as in castrate adrenalectomized animals. The percentage difference between the prostate weights of these two groups was appreciable but the absolute difference was not impressive. The rate of atrophy was much greater in the castrated 26-day old rat with implanted adrenal than in a group of similar rats reported in a previous set of experiments by the same authors which had been castrated but not adrenalectomized.[32] Since cortical substances were not readily available at the time of these studies, the inclusion of adrenalectomized castrate controls treated with cortical steroids was not possible. In using the rate of atrophy of the prostate as an indicator and with the relatively small difference in the rate of atrophy, this control seems to us to be very important. An attempt to compensate for its absence by using prostate/body weight ratios does not seem satisfactory. For the reasons stated above, it seems unlikely that the suggestion that adrenal androgens remain active after circulation through the liver should be accepted.

Although it has long been assumed that the adrenal secretes a distinct androgen, this has recently been questioned. It seems certain that the presence of adrenal secretions in the body is associated with the presence of androgenic substances. It is not yet determined whether these androgenic substances are the direct result of adrenal secretion or the result of metabolic breakdown of adrenal steroids. The suggested finding of Δ4 androstene-3,17-dione by Romanoff, Hudson, and Pincus[33] in adrenal vein blood of man is supportive evidence for the former viewpoint. Marden and Hopkins[34] have demonstrated that the liver of the rat renders this substance biologically inactive. The final determination of the effect of passing the adrenal venous blood through the liver on androgens resulting from adrenal secretions must await further study and methods.

SUMMARY

A method for converting the adrenal venous blood flow of the left adrenal of the dog from one that is initially and primarily systemic to one that is portal is presented. This method relies on diversion of the adrenal venous blood flow to

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[31] Burrill, M. W. and Greene, R. R. The liver and the adrenal androgen of the rat. Endocrinol., **28:** 874, 1941.

[32] Burrill, M. W. and Greene, R. R. Further studies on the andromimetic function of the immature male rat adrenal. Endocrinol., **26:** 645, 1940.

[33] Romanoff, E. B., Hudson, Perry and Pincus, Gregory. Isolation of hydrocortisone and corticosterone from human adrenal vein blood. J. Clin. Endocrinol., **13:** 1546, 1953.

[34] Marden, Harold E., Jr. and Hopkins, W. J. Personal communication.

the left renal vein with subsequent end to end anastomosis of the renal and splenic veins. Dogs in which the procedure has been successfully performed survived in a relatively normal state despite removal of the contralateral adrenal. Intravenous glucose tolerance tests, serum sodium and potassium levels, and urinary 17-ketosteroid excretion were determined in dogs subjected to bilateral adrenalectomy, to implantation of free adrenal grafts to the spleen and subcutaneous tissue, and in dogs subjected to the adrenal shunting procedure. The results of these studies serve to emphasize the relatively normal state of the animals with successful diversion of the adrenal blood to the portal circulation. The rationale for undertaking the study and its possible practical applications are discussed.

To date five patients with advanced carcinoma of the prostate have undergone the shunting procedure. The results of these cases will be the subject for a future publication.

The authors wish to express their gratitude to Dr. W. W. Scott for his enthusiastic encouragement, his guidance, and his co-operation. These studies were dependent on the interest and environment stimulated by him.

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CORTISONE AND ADRENALECTOMY IN TREATMENT OF STERILITY IN WOMEN WITH ADRENOGENITAL SYNDROME

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The adrenogenital syndrome is caused directly by an overproduction of andronic adrenal hormones. It is usually associated with hyperplasia, more rarely th adrenal tumors, but may also occur without demonstrable gross or histogical changes in the adrenal glands.

When adrenal hyperfunction occurs in utero, the female embryo is profoundly asculinized with hypertrophy of the clitoris and malformation of the external nitalia, producing a clinical picture commonly known as female pseudohermaph- ditism. On the other hand, when hyperfunction begins in late childhood or in lult life, the masculinizing effect is usually less pronounced. These women exhibit excessive growth of hair on the face, trunk and limbs, and are often obese, t, in contrast to Cushing syndrome, there is little if any metabolic disturbance. he urinary excretion of the neutral 17-ketosteroids is elevated. Ovarian func- on is arrested, or at least inhibited, with consequent menstrual disturbance and ability to conceive.

There is prior evidence in the published work of Cahill and Melicow, de Paiva nd others that pregnancy has occurred in women with adrenogenital syndrome llowing corrective adrenal surgery. The authors also have observed 2 such asculinized women, previously sterile, who conceived after adrenal operations.

CASE REPORTS

Case 1. (Beth Israel Hospital No. 217840.) A 28 year old white married woman as first seen on January 20, 1949, complaining of inability to conceive and of xcessive growth of body and facial hair.

The menses had begun at the age of 13 and were always painful, irregular and cant. Shortly thereafter, the patient became aware of increasing hirsutism. She egan to have hot flushes, nausea, vomiting and dizzy spells at the time of men- truation. There was, however, no significant change in fat distribution or in ody weight. After thorough investigation, a diagnosis of adrenal hyperplasia as made in 1943 by Dr. Rita Finkler and Dr. Morris Feldman. The patient was reated with various hormone injections without relief. There was little change n symptomatology until 1948, when the patient began to have chills, fever, ysuria and partial urinary retention. An excretory urogram showed the right idney to be hydronephrotic and much lower in position than the left.

The patient was married in May 1948, but could not conceive despite a normal ctive sex life. Thereupon, she consulted several physicians who informed her

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Read at annual meeting, American Urological Association, New York, N. Y. June 3, 1954.
The authors wish to thank Dr. Ella Fishberg, chemist to Beth Israel Hospital, for her elpful co-operation and Miss Virginia F. Rechnitzer who made the 17-ketosteroid determinations

that she never would become pregnant, because she was in "estrogen imbalance" which did not respond to treatment.

The urinary 17-ketosteroid excretion in December 1948 was 28.3 mg. in 24 hours, and on February 24, 1949, it was 20.0 mg. in 24 hours.

Physical examination revealed a well-nourished woman, not obese, with a gaunt masculine appearance. There was excessive growth of hair on the face, chest and extremities, and the pubic hair had a typical masculine distribution. The breasts were normally developed. Abdominal examination was negative except for a mobile tender mass in the right lower quadrant, which was thought to be a ptotic kidney. The uterus was well developed, and there were no adnexal masses. The blood pressure was 110 systolic, 80 diastolic.

A lumbar perirenal gas insufflation was done at the hospital on March 29, 1949. Laminographic x-rays showed normal adrenal shadows on both sides. Excretory urography revealed ptosis and hydronephrosis of the right kidney.

The patient re-entered the hospital on May 3, 1949, and on the next day the right kidney and adrenal gland were exposed through a lumbar incision. The adrenal appeared normal and a wedge-shaped piece was excised. Hemostasis was secured by fine sutures. On opening the peritoneum, the right ovary was found to be atrophic and the left ovary, cystic. The peritoneum was then closed and a nephropexy performed.

Histological examination showed normal adrenal tissue. After an uneventful convalescence, the patient left the hospital on May 14, 1949. She failed to return for follow-up urinary 17-ketosteroid examinations.

The patient became pregnant in July 1949, two months after partial adrenalectomy, and on April 20, 1950, gave birth to a normal boy. She resumed estrogenic therapy because of scanty painful menstruation and again conceived in October 1951. She was delivered of a normal boy in June 1952. There was scanty lactation with each pregnancy, insufficient for nursing.

The patient was again seen early in 1954, complaining of scanty and painful menstruation, which was unrelieved by estrogen therapy. The urinary 17-ketosteroids on February 5, 1954, were elevated to 26.1 mg. in 24 hours.

Oral administration of cortisone, 50 mg. daily, was begun on February 19, 1954, and continued until March 20, when the dose was reduced to 25 mg. daily. On March 17, the urinary 17-ketosteroids had dropped to 10.7 mg. and 11.8 mg. in 24 hours, and on April 26, 1954, they were 30.1 mg. and 28.8 mg. in 24 hours.

Comment: There is a noncalculable loss of functioning tissue following partial adrenalectomy, which is usually much greater than the amount actually resected. This is due to infarction, necrosis and sometimes infection of the remaining adrenal tissue which has been left in situ. Our earlier observations have shown that excision of hyperfunctioning tissue from one adrenal often was followed by a significant, though often temporary, drop in the urinary 17-ketosteroid excretion. The lack of such crucial data following operation in this patient makes it difficult to assess the role played by the partial adrenalectomy and its causal relationship with the ensuing conception. This case, however, did focus our attention on this aspect.

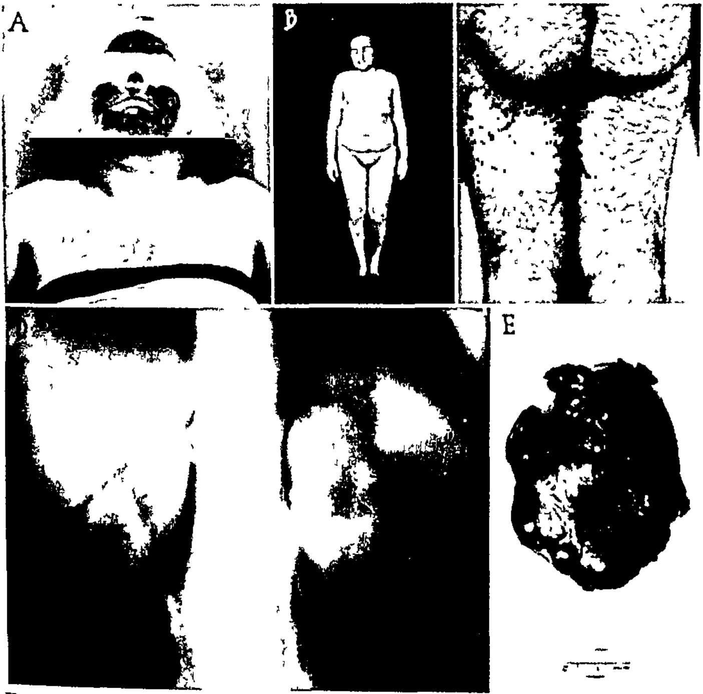

FIG. 1. Case 2. *A*, preoperative. Note acne and excessive hair. *B*, preoperative. Note obesity and hirsu ties. *D*, laminogr shadow of adren adenoma.

Shortly thereafter, Wilhelm and Kamens studied the following case in which the evidence appeared more conclusive.

Case 2. (Beth Israel Hospital Case No. 223391.) A 28 year old white married woman was first seen on September 12, 1949, complaining of inability to conceive, excessive growth of facial and body hair, and scanty menses. She had gained 35 pounds. The symptoms had begun 3 years before and had become progressively worse. The patient reported normal sexual activity but had never become pregnant.

Physical examination revealed an obese female with a heavy growth of coarse hair over the face, chest, back, buttocks and thighs (fig. 1, *A*, *B*, *C*). There was severe facial acne. Pelvic examination showed slight enlargement of the clitoris and moderate hypoplasia of the uterus. No adnexal masses were felt. The blood pressure was 118 systolic, 60 diastolic.

An excretory urogram revealed the left kidney to be lower than the right.

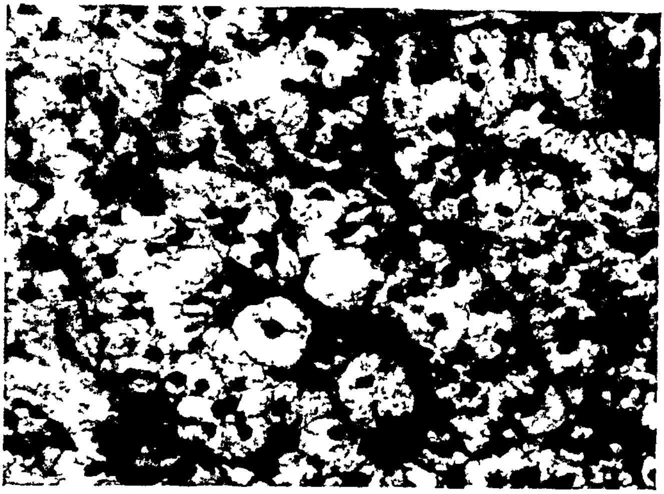

FIG. 2. Case 2. Adrenal adenoma

Bilateral lumbar perirenal air insufflation was done on October 18, 1949. Simple films and laminographic x-rays demonstrated a large mass in the left suprarenal region. The right adrenal shadow was normal (fig. 1, *D*).

The urinary 17-ketosteroids on October 18 were 55.9 mg. in 24 hours and a glucose tolerance test showed a diabetic curve.

On October 25, 1949, a large tumor of the left adrenal gland was exposed and totally excised (fig. 1, *E*). The pathological report revealed adrenal adenoma, measuring 7 by 5 by 5 cm. and weighing 56.0 gm. No normal adrenal architecture remained (fig. 2).

The postoperative course was complicated by a left pneumothorax and a pleural effusion which responded promptly to treatment. On November 15, the urinary 17-ketosteroids were 1.2 mg. in 24 hours. The patient left the hospital on December 1.

She became remarkably feminized, much of her facial and body hair fell out, her weight decreased and her acne improved. The menses returned to a normal cycle with increased flow. Four months after operation, there was little residual hirsutism and only mild acne (fig. 3). Glucose tolerance tests were now in the

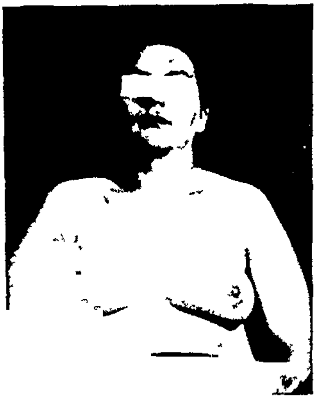

FIG. 3. Case 2. Four months after operation. Note feminine contours and absence of acne and hirsutism.

normal range The urinary 17-ketosteroids on December 27 were 6 4 mg in 24 hours, and on January 30, 1950, were 8 9 mg in 24 hours

The patient conceived in February 1950, approximately 3½ months after excision of an adrenal adenoma Pregnancy was uneventful and on October 2, 1950, a normal boy was born

Comment: A differential diagnosis between adrenal hyperplasia and neoplasm can best be made by simple x-rays following perirenal gas insufflation combined with laminographic (tomographic) studies In case 2, this technique definitely established the presence of a left adrenal tumor and also sharply delineated a normal right adrenal shadow

The urinary 17-ketosteroids, which were greatly elevated before operation, fell precipitately to subnormal levels immediately after excision of the adrenal adenoma and then gradually returned to normal levels Shortly thereafter, this patient conceived

Cortisone therapy Wilkins and his co-workers have shown that the administration of cortisone in cases of congenital adrenal hyperplasia is followed by feminization and a reduction of the 17-ketosteroid excretion in the urine They have offered the theory that cortisone inhibits the secretion of ACTH by the pituitary and thus puts the hyperactive adrenal at rest With suppression of adrenal gland activity, the adrenal androgen and estrogen secretion is greatly decreased This permits the elaboration and secretion of pituitary gonadotrophins, which cause maturation of the ovary and the establishment of normal genital development

If, on the other hand, the adrenogenital syndrome is caused by an adrenal neoplasm, the urinary 17-ketosteroid excretion is not affected by the administration of cortisone This disparate reaction to cortisone has been used as a differential diagnostic test between adrenal hyperplasia and tumor

The treatment of adrenogenital syndrome caused by tumor is, of course, operative On the other hand, in cases due to adrenal hyperplasia the administration of cortisone appears at the present time to give better results than surgery. Inability to conceive is a not uncommon complaint of such virilized women, and it occurred to us that it might prove worthwhile to employ cortisone in order to feminize and develop these women and make them susceptible to impregnation

Case 3 (Beth Israel Hospital No 271806) A 29 year old woman consulted us on August 8, 1953, complaining of inability to conceive She was first seen in 1944, when she complained of an excessive growth of facial and body hair for 1½ years, menstrual irregularity for 2 years, and obesity

The menses began at the age of 11, and were regular at 30-day intervals until 16, when she had amenorrhea for 3 months followed by several regular periods. Menstrual irregularity then recurred and had persisted The flow, when present, was normal in quantity and character

Physical examination in 1944 revealed generalized obesity, she weighed 154 pounds and was 63 inches tall There was an excessive growth of hair on the face, neck, chest and breasts The pubic hair distribution was masculine The breasts were underdeveloped and there were abdominal striae The blood pressure was 160 systolic, 70 diastolic

Lumbar perirenal air insufflation was done at the hospital on March 18, 1944. Laminographic x-rays revealed normal adrenal shadows on both sides. Skull x-rays showed no abnormality of the sella turcica. The urine showed some sugar after a glucose tolerance test and the 17-ketosteroids were elevated to 71.3 mg. in 24 hours.

After leaving the hospital the patient was given thyroid extract without change in weight or any improvement of the menstrual irregularity. She was married on December 10, 1944. Pelvic examination in February 1945 revealed a small uterus with no adnexal masses.

The patient was not seen again until August 1953. During these 8½ years she had undergone investigation for sterility by several gynecologists and had been told that she was in "glandular imbalance." Repeated courses of thyroid extract and estrogens were administered without result.

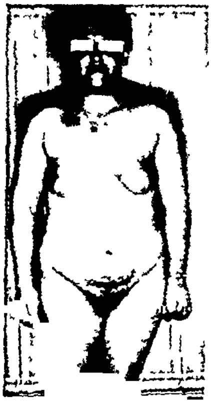

FIG. 4. Case 3. Prior to cortisone therapy showing hirsutism and obesity

Physical examination in 1953 revealed increased obesity; she weighed 175 pounds. The blood pressure was 142 systolic, 60 diastolic. The urine was negative. The patient still complained of hirsutism and irregular menstruation (fig. 4).

A presacral air insufflation was done at the hospital on September 14, 1953. Laminographic x-rays revealed normal adrenal shadows. The urinary 17-ketosteroids were 18.6 mg. in 24 hours.

The administration of oral cortisone, 25 mg. daily, was begun on September 16. The dose was increased to 50 mg. daily on September 29, and continued until November 19. The weight dropped from 175 to 167 pounds. The patient had a normal menstrual period on October 28. This proved to be her last period.

The urinary 17-ketosteroids on November 7 had fallen to 13.5 mg. in 24 hours, and, shortly thereafter, the patient was impregnated. On November 19, cortisone was reduced to 25 mg. daily, but on December 9, the daily dose was increased to 37.5 mg. because of the patient's failure to lose weight.

On January 4, 1954, she was examined by her obstetrician, who found her to be about 10 weeks pregnant. On his advice and without our knowledge, cortisone was discontinued from January 4 to January 10. Following the temporary cessation of cortisone therapy, the urinary 17-ketosteroids on January 17 had risen to 23.8 mg. in 24 hours (fig. 5).

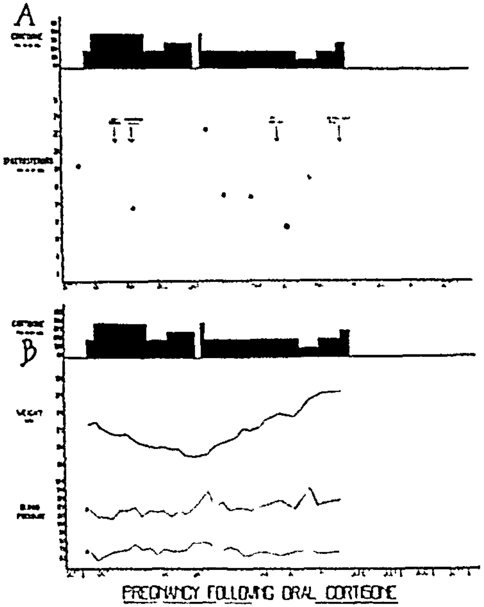

FIG. 5. A, showing relation of 17 ketosteroids to cortisone. B, showing relation of weight and blood pressure to cortisone.

Cortisone, 50 mg. daily, was resumed on January 11, and reduced to 25 mg. daily on January 13. The dosage was continued until April 14, when it was experimentally reduced to 12.5 mg. daily.

The urinary 17-ketosteroids on February 2 were 14.3 mg. and 15.8 mg. in 24 hours, and on March 3, 14.0 mg. and 15.7 mg. in 24 hours. On April 1, the 17-ketosteroids were 10.6 mg. and 11.7 mg. in 24 hours.

On April 14, the daily dose of cortisone was reduced to 12.5 mg. and on April 26, the 17-ketosteroids had risen to 18.5 and 16.0 mg. in 24 hours.

The patient was again examined on May 1. She now weighed 185½ pounds and showed external evidence of pregnancy. The hirsutism was unaffected. Cortisone, 25 mg. daily, was resumed. The urinary 17-ketosteroids on May 18 were 16.9 and 17.1 mg. in 24 hours. On May 21, 1954, the daily dose of cortisone was raised to 37.5 mg.

The patient went into labor on May 23 and on May 25 gave birth to an apparently normal premature female baby, weighing 2 pounds, 6 ounces. Three days later, the infant died.

The following is a summary of the findings in the baby girl, Mt. Sinai Hospital Autopsy No. 16050 (Dr. Lotte Strauss): Prematurity (weight at autopsy, 850 gm.), subependymal, intraventricular and subarachnoid hemorrhage, bilateral adrenal hemorrhage, and necrosis of fetal cortex, generalized icterus, minimal aeration of lungs, focal aspiration of amniotic sac contents, immaturity of lung, focal acute pneumonia; congestion of liver and kidneys; petechiae of bladder; erosions of gastric mucosa; no congenital malformations.

The finding of intracranial and adrenal hemorrhage of varying extent is not uncommon in premature newborns and is probably related to a state of shock due to anoxia. On the basis of my findings, I cannot say that the mother's treatment with cortisone had any deleterious effect on the baby. It seems to me that these findings are related to the infant's premature state.

Comment: Oral cortisone was administered to a 29 year old woman suffering from adrenocortical hyperfunction who had been unable to conceive in almost 9 years of marriage. The urinary 17-ketosteroid excretion, formerly elevated, was reduced to normal levels. Shortly thereafter, this patient conceived. No similar case report has been found in a review of the literature. Kupperman recently reported that cortisone did not prevent pregnancy in a normal 22 year old woman who was treated for post-traumatic contracture of the hand. The cortisone was administered for only 2 months and apparently did not interfere with the progress of the pregnancy or have any effect on the offspring.

SUMMARY

Inability to conceive was the chief complaint of 3 hirsute women suffering from adrenogenital syndrome. Two became pregnant shortly after surgical intervention; the first followed partial adrenalectomy, and the second, excision of an adrenal adenoma.

The third patient was treated with oral cortisone. The urinary 17-ketosteroids were soon reduced to normal levels and, shortly thereafter, impregnation occurred.

This brief experience and that of others indicates that sterility in women, caused by androgenic adrenocortical hyperfunction, may at times be reversible. The cases caused by neoplasm require surgical excision. On the other hand, those due to hyperplasia or hyperfunction may properly be treated with cortisone.

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HORSESHOE KIDNEY WITH UNILATERAL REDUPLICATION OF THE PELVIS AND URETER AND URETERAL ECTOPIA

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Although anomalies of the upper urinary tract are comparatively rare, they are of clinical significance, since they predispose to obstruction, stasis, impairment of renal function and infection. Guiterrez estimated that 40 per cent of all pathologic conditions of the upper urinary tract are due to congenital anomalies. Such anomalies have been found in 3.7 per cent (Smith) of consecutive urologic hospital admissions and in 9.6 per cent of consecutive patients on whom pyelograms were obtained (Dees).

Among the rarer abnormalities is the horseshoe kidney with ureteral ectopia. Only 3 such cases have been found in the literature; in two, the left ureter ended in the colliculus seminalis (Thom) and in the other one it ended in the vestibule (Massari). All 3 cases were discovered at necropsy. The following is believed to be the first recorded case to be recognized clinically and treated.

CASE REPORT

W. L., a Chinese girl, aged 20 months, had had an inconstant yellowish vaginal discharge and intermittent fever for 4 months. Several courses of antibiotics for pyuria, frequency and painful voiding had resulted in only temporary relief.

Physical examination revealed an irritable, weak and underweight baby girl with no definite mass, tenderness or rigidity. Pus (grade 3) with gram negative bacilli was found in the urine (Proteus); blood chemistry studies yielded normal values.

On May 22, 1952 cystoscopy under general anesthesia revealed mild diffuse cystitis with normal ureteral orifices. No. 4 catheters were easily passed up each side but the urine scarcely dripped from either side. The intravenous injection of indigo carmine proved unsatisfactory. Retrograde urograms revealed a normal right kidney except for medial deviation of the lower pole. The left kidney was malrotated, low and more lateral in position than normal. Investigation of the urethra revealed a slit-like opening on the floor of the urethra, distal to the bladder neck, and hidden by a fold of mucous membrane. A number 6 catheter was easily passed up this opening and a copious amount of white fluid drained. The three catheters were injected and the urogram showed the large catheter coiled back of the bladder and communicating with an elongated, tortuous tube, alternately dilated and constricted, and apparently connected with the left pelvis (fig. 1). Further injection of dye identified the tube as a ureter draining a large hydronephrotic upper left pelvis (fig. 2). The diagnosis was then obvious. B. Proteus was recovered from culture of the urine from the ectopic ureter.

Read at annual meeting, Southeastern Section, American Urological Association, Havana, Cuba, March 26–29, 1953.

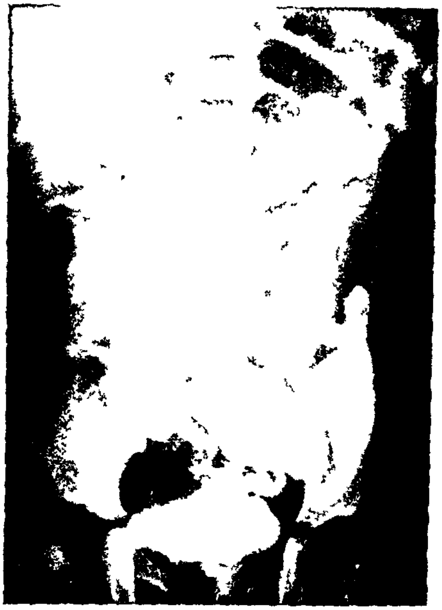

FIG 1

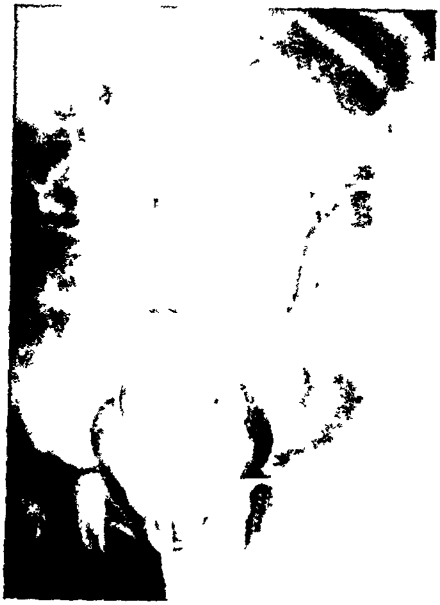

FIG. 2

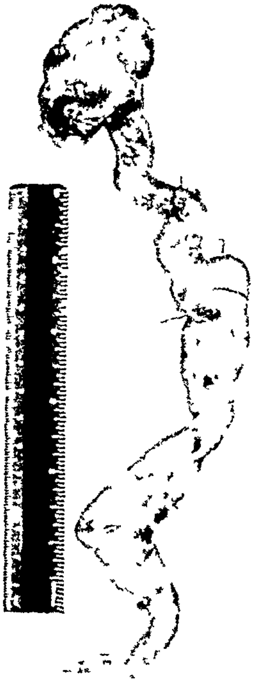

FIG 3

Left heminephrectomy and complete ureterectomy were performed on May 26, 1952 through an incision in the loin extending to the lower left quadrant. The upper segment of the kidney presented a thin, irregular cortex and a dilated pelvis. The ureter was wound about the pedicle of the lower pole and was densely adherent to the peritoneum in several places. The wall of the lower ureter merged with the base of the bladder and had to be separated by sharp dissection. The ureter was severed at its junction with the urethra and the defect closed with interrupted double 0 chromic sutures (fig. 3). Convalescence was uneventful and urinalyses had yielded negative results.

Microscopic sections showed atrophy of the medullary portions of the kidney, infiltration of the medulla and parts of the cortex and large numbers of lymphocytes. The glomeruli and tubules were otherwise normal. The walls of the ureter which were thick and fibrous showed lymphocytic infiltration.

DISCUSSION

The incidence of horseshoe kidney is said to occur once in every 600 to 1800 cases. Of 117 horseshoe kidneys observed at autopsy, reduplication of ureters occurred in 10 cases (Campbell). In 15,919 autopsies in children ectopic ureters occurred in 10 cases (Campbell). It is believed, however, that the incidence of ectopic ureters is higher, especially in males.

Ureteral ectopic orifices may be small but they are usually large and often slitlike. The ureter above is dilated, tortuous and thin. Although infection occurs in practically every case, the dilatation is believed to be partially the result of faulty neuromuscular development. The pelvis may be small but it is usually dilated and infected. The corresponding renal segment is usually hypoplastic with pyelonephritis or pyonephrosis (Bacon). When seen, it is frequently functionless..

In ureteral ectopia in females the urinary symptoms are prominent. The opening is usually beyond the control of the internal sphincter and as a consequence there is frequently a constant dribble of urine, which is present in spite of normal voidings. In incontinent female infants this is usually overlooked until complications indicate thorough urologic study. The dribbling may be intermittent, diurnal or nocturnal. It may occur only when standing, coughing, sneezing or straining. It may be absent for long periods, or it may occur for the first time after childbirth when the sphincteric action has been altered. The leakage of urine causes cutaneous irritation, which, in growing children and women, produces psychic trauma of varying degrees. Such trauma is commonly associated with shyness, reticence and an aversion to marriage.

Infection is a common complication and it may produce, as the only clinical manifestation, a purulent urethral or vaginal discharge (Crenshaw). In females, careful inspection and probing must be focused on the vestibule, especially around the urethral orifice, the superior vaginal vault and the area adjacent to the cervix. The orifice may be hidden by a fold of mucosa (Howard) or it may be surrounded by granulations (Moore). Examination of the urethra and bladder base with a panendoscope or Braasch direct vision scope is an essential diagnostic procedure.

Excretory urography has been considered the most valuable single aid in the diagnosis of ureteral ectopia in duplicated pelves and ureters (Crenshaw). It furnishes valuable data on the function of the involved side and, equally important, gives information on the presence and function of the opposite kidney.

The treatment of horseshoe kidneys and duplicated pelves and ureters consists in treatment of the complications. In ectopic ureters the treatment of choice is heminephrectomy and ureterectomy. If the opposite kidney functions satisfactorily the pathologic segment of the kidney draining into the ectopic ureter should be removed with the ureter. All infected, dilated ectopic ureters and all ectopic ureters opening into the urethra should be removed completely; in the former instance, a pyo-ureter may develop whereas in the latter a urethral diverticulum may result.

SUMMARY

A case is presented of horseshoe kidney with unilateral duplication of the pelvis and ureter, and ureteral ectopia, which is believed to be the first recorded case to be recognized and treated. Only 3 other cases were found in the literature, all of which were discovered at necropsy. Ectopic ureter ending in the urethra should be removed completely to prevent development of a urethral diverticulum.

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FORMATION OF URIC ACID CALCULI DURING CHEMOTHERAPY FOR LEUKEMIA

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The formation of uric acid calculi in the urinary tract, during chemotherapy for leukemia, may present a urologic problem of significance and importance. The incidence of uric acid calculi in general hospital population has been calculated to be 0.07 per cent, while in leukemia an incidence of 4.67 per cent has been reported. *Renal calculus formation, during the treatment of leukemia with* nitrogen mustard-like compounds, may occasionally be so extreme as to cause complete obstructive uropathy, uremia and death. However, it is a condition which has received but slight attention among urologists. Its course is rapid and demands dramatic action to prevent the inevitable. It is the purpose of this paper to point out the possibility of urologic or renal complications, following administration of these nitrogen mustard-like compounds, in the treatment of leukemia and to prevent the occurrence of calculi during therapy.

It is well known that in leukemia, an elevation of serum uric acid and an increased excretion of uric acid may occur. Uric acid is one of the chief end-products of purine catabolism. There is evidence that potent therapeutic agents, used in the treatment of leukemia, can produce excessive breakdown of nucleoproteins which, excreted with urine, may result in the precipitation of urates and uric acid in such amounts as to produce obstructive uropathy.

It also has been demonstrated that calculi may develop in certain individuals who have leukemia but who have not been under treatment. Such a development results from excretion of excessive amounts of uric acid with the formation of calculi in certain instances which may be so extreme as to cause obstruction in the ureters. It has been shown as well, that the administration of nitrogen mustard-like chemotherapeutic compounds, in certain individuals, may cause the formation of uric acid calculi. The formation of similar calculi has been reported in certain individuals with leukemia following x-ray therapy. As a consequence, irradiation on one hand and chemotherapeutic compounds on the other cannot be considered as therapeutic agents in the treatment of leukemia without consideration of their potential dangers. It is obvious that increased serum acid is a constant factor in leukemia. It also is apparent that anything which alters the solubility of the uric acid in the urine may cause its precipitation.

It is a matter of record that the administration of carcinolytic compounds is not followed by uric acid calculus formation or uremia in every instance. The literature is too fragmentary to arrive at any percentage conclusion at this time but it is recognized that such a complication develops on occasion. Consideration of the recognized data reflects that serum uric acid levels are known to be elevated in leukemia, that x-ray therapy may cause a precipitation and crystalization of uric acid and that the administration of certain nitrogen mustard-like compounds

Read at annual meeting, Mid-Atlantic Section, American Urological Association, Washington, D. C. April 22, 1954.

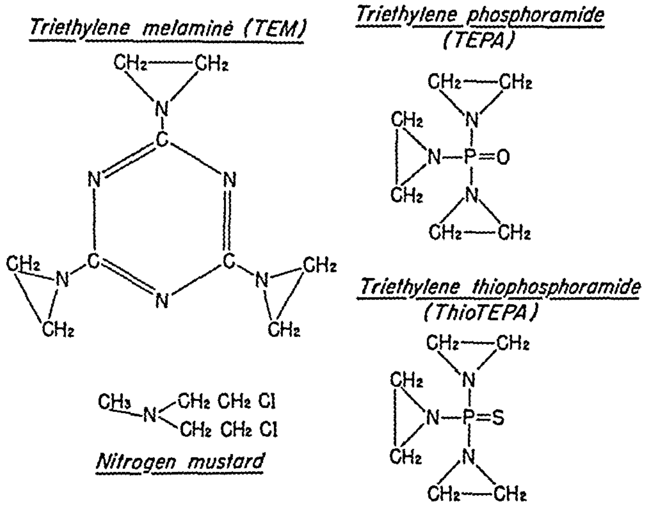
Triethylene melamine (TEM)
Triethylene phosphoramide (TEPA)
Triethylene thiophosphoramide (ThioTEPA)
Nitrogen mustard

FIG. 1. Structural formulae of triethylene melamine (TEM), triethylene phosphoramide (TEPA) and triethylene thiophosphoramide (thio-tepa) as compared with the formula of nitrogen mustard.

may cause excretion of uric acid beyond urinary solubility with the formation of uric acid calculi with possible ureteral occlusion.

Intensive treatment by certain chemotherapeutic compounds of the nitrogen mustard-group may cause an excessive nucleoprotein breakdown so that the amount of uric acid excreted exceeds the urinary solubility. When such a state occurs there is a deposition of uric acid in the collecting tubules of the kidney or in the ureters. This occurs when the urine solubility is exceeded which may result when the urinary volume is not adequate or when the solubility of uric acid is decreased by acidification of the urine. The deposition of uric acid crystals within the tubules or calculi within the calyces, renal pelvis or ureters may be so extensive as to cause total occlusion with resulting uremia and death. The case to be reported illustrates this fact.

Those nitrogen mustard-like compounds most commonly used in the chemotherapy of leukemia are triethylene melamine (TEM), triethylene phosphoramine (TEPA), and triethylene thiophosphoramine (Thio-TEPA) (fig. 1).

TRIETHYLENE MELAMINE (TEM)

Many compounds have been synthesized since the introduction of nitrogen mustard in 1943 as a chemotherapeutic agent for disseminated malignant lymphomas. Among these newer compounds is triethylene melamine (TEM). It is effective after oral administration, is less toxic than nitrogen mustard and causes less nausea and vomiting.

TRIETHYLENE PHOSPHORAMIDE (TEPA)

Further studies in drugs having carcinolytic properties led to a survey of another compound, triethylene phosphoramide (TEPA) which showed an effect on mammary adenocarcinoma and against certain forms of leukemia.

TRIETHYLENE THIOPHOSPHORAMIDE (THIO-TEPA)

Another compound used in the treatment of chronic leukemia is triethylene thiophosphoramide (Thio-TEPA). This compound appears to have its most favorable action in subacute and chronic leukemia but it is not a cure. Triethylene thiophosphoramide (Thio-TEPA) differs from triethyline phosphoramide (TEPA) only in the replacement of a double bond oxygen atom in a molecule of a sulfur atom. This difference appears to contribute some change in action if the sustained beneficial effects of triethylene thiophosphoramide (Thio-TEPA) in the treatment of patients with chronic leukemia is compared with the very limited response of similar patients treated with triethylene phosphoramide (TEPA).

It is imperative that when such compounds are administered, adequate fluid intake and output be continued to maintain solubility of the urine. Even then the excretion of uric acid may be so excessive that calculus formation is inevitable in some individuals. Alkalization of the urine should be maintained as the solubility of uric acid is increased in alkaline urine but is decreased in acid urine. The creation of uric acid calculi is less likely to occur when a high pH of the urine is maintained.

Attention is directed to the chronological dates of the drop in the leukocyte count, the rise of the blood urea nitrogen and the levels of serum uric acid of a patient with chronic leukemia whose illness and treatment illustrate several pertinent and important significant factors.

CASE REPORT

M. D., a white woman aged 60, was admitted February 7, 1953 with a diagnosis of chronic granulocytic leukemia. She gave a history of gradual, increasing blurring of vision beginning 4 weeks prior to admission. She was very weak, and complained of a headache, occasional vomiting and dizziness to the extent that she was unable to hold her balance. There was constant tinnitus. She had received no treatment since the onset of the disease except the administration of two blood transfusions.

Urinalysis: clear, specific gravity 1010, pH 6.0, very faint trace of albumin, occult blood negative, 1–5 leukocytes. Complete blood count: hemoglobin 8.5 mg., red blood cells 1,980,000; white blood cells—700,000. Triethylene thiophosphoramide (Thio-TEPA) 20 mg. was administered intravenously on February 10, 1953. Triethylene thiophosphoramide (Thio-TEPA) 30 mg. was administered intravenously on February 11, 1953. White blood cells—745,000. Triethylene thiophosphoramide (Thio-TEPA) 15 mg. was administered on February 12, 1953. Vision returned, was considered normal. Urinalysis February 13, 1953, moderately cloudy, very faint trace of albumin, 225–250 red blood cells per high power field. Urinary retention developed; total of 1900 cc removed by two catheterizations. The patient rapidly became toxic. Serum uric acid 10.4 mg. Blood urea nitrogen 17 mg; serum uric acid 9.2 on February 14, 1953. Pain developed in the left upper abdomen and loin; urine scanty, but concentrated. X-ray of the kidney, ureters and bladder negative for calculi. White blood cells—220,000;

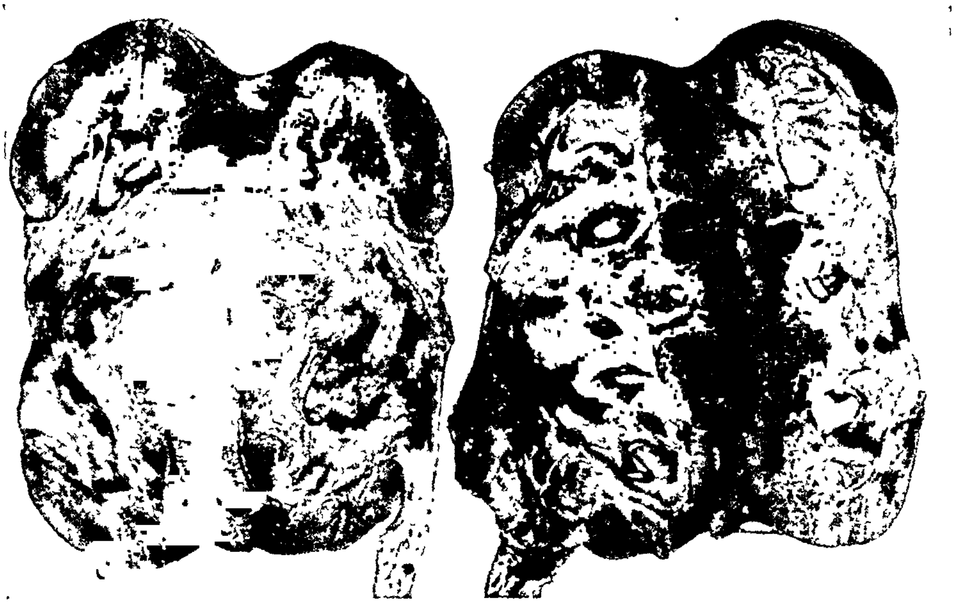

FIG. 2. Note gritty mass within several calyces. Also note size of ureters.

urinary output was markedly reduced. Blood urea nitrogen 105 mg., plasma CO_2 25.6 volumes. On February 18, 1953 ureteral catheterization was attempted but was unsuccessful because of massive edema of trigone. Multiple submucous hemorrhages were visualized throughout the entire vesical mucosa. Blood urea nitrogen 135 mg. White blood cells 155,000; output 36 cc. On February 20, 1953, white blood cells 48,600; blood urea nitrogen 140 mg; output 200 cc in 24 hours. Attempted ureteral catheterization again unsuccessful. White blood cells 39,600; blood urea nitrogen 185 mg.; output 170 cc on February 21, 1953. Coma developed February 22, 1953; death ensued February 24, 1953.

Autopsy report in part stated that, "There is well defined granularity within the renal pyramids which is similar in nature to the uric acid crystals noted in the lower urinary tract. The calyceal walls are also gritty in texture (fig. 2). The ureters externally are dilated to several times their normal size. . . . A probe passed from the bladder into each ureteral orifice elicits crepitation secondary to contact with uric acid concretions. Longitudinal section discloses complete ureteral obstruction by these varying sized calculi many of which are grouped in large irregular clusters (fig. 3). Uremia secondary to bilateral ureteral obstruction by uric acid sediment resulting from rapid leukocytic destruction in triethylene thiophosphoramide (Thio-TEPA) treated chronic myelogenous leukemia."

This case illustrates the rapid breakdown of nucleoproteins with an overwhelming formation of uric acid calculi following the administration of possible carcinolytic compounds. The patient exhibited a marked elevation of blood uric acid and beyond question had some ureteral obstruction due to uric acid calculi before treatment with triethylene thiophosphoramide (Thio-TEPA) was begun. It is hardly conceivable that dilatation of the ureters and calyces, exhibited at

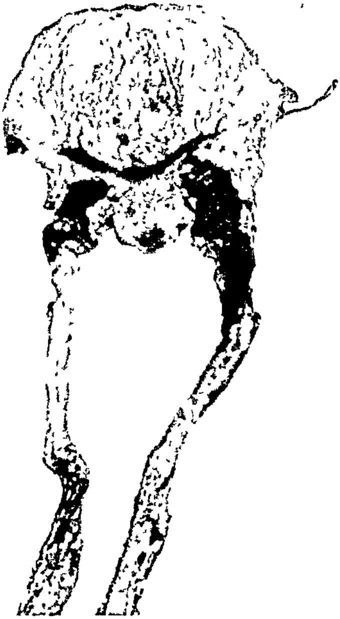

FIG. 3. Specimen: bladder and ureters. Note mass of gritty material and calculi in lower dilated ureters.

the time of autopsy, could have occurred within two weeks. Undoubtedly, calculi had been present in the ureters but the administration of the chemotherapeutic agent hastened the breakdown of the nucleoproteins with the formation of excessive uric acid with the resultant occlusion of the uriniferous tubules and the ureters.

The case report also illustrates the drastic and rapid fall of the leukocytes following administration of nitrogen mustard-like compounds, in this instance triethylene thiophosphoramide (Thio-TEPA). Also, it illustrates a known fact that patients with leukemia have elevated serum uric acid as a component of the disease.

CONCLUSION

It is a well established and acknowledged fact that the excretion of uric acid in the urine is increased in leukemia.

It is also an established fact that uric acid calculus formation may be so extensive as to produce uremia by the occlusion of the renal tubules and/or the ureters even without treatment. This is more apt to occur in the presence of acid urine.

In some instances the treatment of leukemia by nitrogen mustard-like compounds may cause increased uric acid excretion beyond urinary solubility causing complete occlusion of uriniferous tubules and/or the ureters with resulting uremia and death.

High intake of fluids should be maintained throughout therapy. Alkalization of the urine should be established and maintained as alkaline urine increases the solubility of uric acid.

It is suggested that an excretory urogram should be made before administration of the nitrogen mustard-like compounds for treatment of any condition, particularly leukemia; that daily serum uric acid determination be done as well as daily determination of blood urea nitrogen; and that a constant intake and output record be constantly maintained during and after treatment. Any alteration of these tests should be followed by ureteral catheterization and irrigation of the pelvis with an alkaline solution. It cannot be determined prior to administration of these compounds whether calculi will develop in a given individual. It is only by constant surveilance of the patient under treatment that the presence of calculi can be suspected or detected. If marked alteration of blood chemistry has occurred it may be impossible to prevent the inevitable.

I am indebted to Dr. Harry Shay, Temple University School of Medicine and Hospital, for permission to prevent the case history.

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FOREIGN BODY IN THE LEFT KIDNEY AND URETER

BELA GONDOS

Foreign bodies of the upper urinary tract are rare. A review of the 32 case reports in the literature has been given in a recent article by Osmond.

A good classification of foreign bodies of the upper urinary tract may be given by the route through which they reach these organs, the most common of which is the external injury. These injuries are mostly inflicted by bullets or particles of explosives. There are also reports of needles penetrating into the kidney from the outside. In this group should also be listed the 3 cases of rubber tubes, which became foreign bodies as the result of surgical procedure. The second route, in order of frequency, is the gastro-intestinal canal, from which foreign bodies can penetrate into the upper urinary tract by perforation. Eleven such cases have been reported, needle, bobby pin, tooth pick, paper clip, hair pin, and fish bone having been found on operation. The location of the perforation is most commonly the second portion of the duodenum, the curvatures of which cannot be passed easily by long, stiff objects; the right kidney is involved in this case. In a smaller number of cases the probable portal of penetration was the colon. In 2 cases the right colon, in one occasion the left half of the colon, was considered to be responsible. The third, and less common way, is claimed to be a retrograde migration of the foreign body from the lower urinary tract. Small objects, pushed into the urethra and reaching the bladder following masturbation, playing, or accidents, have been described in this group. It is assumed that antiperistalsis of the ureter may bring these objects into the higher segments of the urinary tract.

Foreign body of the upper urinary tract is only exceptionally silent. Infection is generally associated with this condition, fever, general malaise, and pain being the most common presenting symptoms. Urinalysis may show pyuria and hematuria. Elicitation of the respective historical data is of utmost importance in the diagnosis. X-ray examination may reveal the opaque foreign body if it is metallic in nature, or may show a concrement, i.e., an incrustation of calcium salts around the foreign body. A rubber tube, if large enough, may also cast a visible shadow. In one fifth of the cases reported, a diagnosis of foreign body could be made only by surgical exploration.

The proper treatment is removal of the foreign body; subsidence of the infection cannot be expected without this procedure. If a conservative operation is not feasible, nephrectomy should be performed.

CASE REPORT*

A 70 year old man had a 2 week's history of fever and chills, as well as pain in the left flank. On physical examination a large, indefinite mass was palpable

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* This case was observed in the Szasz-Gruenwald Sanatorium, Budapest, Hungary, on May 8, 1941. Operation was performed by the late Dr. Henrik Szolos.

in the left kidney region; the patient indicated considerable tenderness in that area on palpation. Marked pyuria was present. Excretory urography failed to visualize the urinary passage-ways on the left. Following this examination left ureteral catheterization and retrograde pyelography were performed. After introduction of the ureteral catheter, purulent urine passed. On pyelography 17 cc of contrast material was instilled without any resistance. Pyelograms revealed a moderate dilation of the calyces and the kidney pelvis; there was absence of the normal papillary impressions of the calyces. In the projection of the lower pole of the kidney shadow and distal to it, a round cavity having the size of a child's fist was filled by opaque material; it was located just lateral to the ureter. There were two projections of the opaque shadow extending from the area of the lower calyx, which were considered due to back flow of the contrast material into the tubules. No direct communication of the round cavity with the pelvio-calyceal system or with the ureter could be visualized. The density of the opaque material in the cavity was considerably less than that in the kidney pelvis or in the calyces, suggesting that it became diluted by urine, pus, or both. Our impression was that the patient had pyonephrosis on the left side and also an abscess cavity, which was communicating with the upper urinary passage-ways.

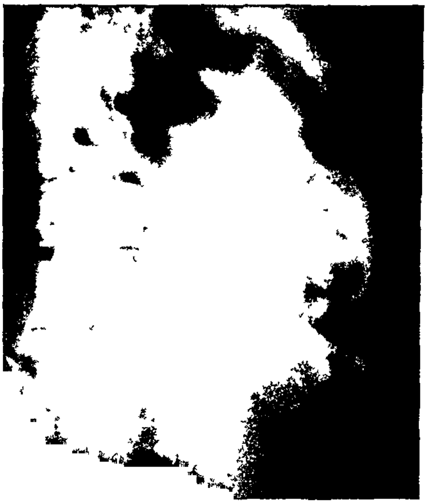

FIG. 1. Extravasation of contrast material into the abscess cavity from upper urinary passageways through perforation of fish bone, which was not visualized on the x-ray film.

Surgical exploration disclosed a large inflammatory mass which included the adjacent ureter and the peritoneum. In preparation of the lower pole of the kidney, an abscess cavity, the size of a medium apple, was opened. The abscess was located in the adipose capsule and was bounded by the ureter and the fibrous capsule of the kidney. Nephrectomy was performed. Examination of the surgical specimen showed that the kidney was largely a pyonephrotic sac. A bean sized calculus and a fish bone, measuring 6 cm. in length and approximately 2 mm. in thickness, were found in the pyonephrotic cavity. The fish bone had penetrated the kidney, its end being located in a perforated opening of the ureteral wall. The operation resulted in complete recovery. A thorough history postoperatively failed to elicit any reference to the swallowing of a fish bone.

COMMENT

Despite the negative history, the only reasonable explanation is that the patient swallowed a fish bone which reached the left half of the large bowel and perforated its wall; the foreign body then entered the adjacent left ureter and the lower pole of the left kidney. The perforation resulted in infection of the kidney cavity and in destruction of the kidney substance. Through the perforation of the ureter extravasation of the urine took place and subsequently an abscess of the adipose capsule developed. This abscess cavity was visualized by opaque material escaping from the ureter through the perforation. The foreign body itself was not visualized on the x-ray film.

DISCUSSION

Ten such cases of foreign body in the upper urinary tract are recorded in the literature, and are interpreted as the result of *perforation from the alimentary canal*. Nine of these occurred on the right and only in 1 case was the foreign body on the left side (Fricke). This was the case of a 55 year old man, who was admitted with left flank pain of 8 days' duration. Urologic examination revealed complete obstruction of the left upper ureter and a tentative diagnosis of an obstructing ureteral stone was made. On surgery, a small perforation of the left ureter and on the adjacent peritoneum was discovered. Extensive adhesions involved the ureter and the peritoneum and between these a small abscess cavity was found. A fish bone, having the dimensions of 5 cm. in length and 1 mm. in thickness, was discovered in the abscess; the end of the fish bone was still in the ureter. Around the perforating fish bone the mucous membrane of the ureter was infiltrated to such a degree that the ureteral lumen became completely obstructed. No stone was found. The patient had a history of swallowing a fish bone 8 days prior to admission. This fish bone apparently passed the duodenum and after arriving to the region of the splenic flexure, had perforated the wall of the colon. To this report of the literature another case of foreign body in the left kidney may be added, in which the possibility of similar route of penetration was raised (Blaine). The foreign body was a broken sewing needle surrounded by a concrement; both needle and the concrement were visualized on the x-ray films. It was thought that the needle, after entering the urethra, reached the kidney pelvis by retrograde migration. A discussant suggested the intestinal tract as the portal of entrance; evidence of perforation had, however, not been found.

Our case is considered the second (possibly the third), in which a foreign body in the left upper urinary tract was found and in which the area of penetration was considered to be the intestinal tract. The pathological findings are similar to those published in Fricke's case Even the inflicting foreign body was a fish bone in both cases. In our patient, however, the abscess cavity visualized by opaque material indicated a perforation of the upper urinary tract. Though the correct diagnosis could be better approached, no suggestion of foreign body was raised prior to surgery.

SUMMARY

A case of fish bone in the left kidney and ureter, supposedly penetrating from the colon, has been presented. On x-ray examination, an extravasation of the opaque material around the lumbar ureter was visualized. The fish bone did not cast a visible shadow on the x-ray film. The respective literature is discussed.

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LOWER URINARY TRACT IMPLANTS OR METASTASES FROM CLEAR CELL CARCINOMA OF THE KIDNEY

JOHN E. HESLIN, WILLIAM A. MILNER AND WILLIAM B. GA[illegible]

From the Department of Urology, Albany Hospital and Albany Medical College, [illegible]

Two cases of clear cell carcinoma of the kidney, with implants or [illegible] the ureter and bladder, have prompted the discussion of this subject, [illegible]ing of the cases and the suggestion that, possibly, our surgical procedure [illegible] handling of parenchymal tumors may need revision in certain cases.

The consideration of the implantation of tumor cells in the ureter, [illegible] and the urethra in papillary tumors of the renal pelvis has long been [illegible]tal principle in urological surgery.

McDonald and Priestley[1] in reviewing 75 cases of tumor of the [illegible] operated on at the Mayo Clinic, found 52 of the papillary type, 32 [illegible] these involved the corresponding ureter and 32 per cent the bladder. [illegible]ferred to Strikers' series of 175 cases of papillomatous neoplasms [illegible] pelvis, with 47 per cent involving the ureter and bladder and Caulk[2] suggested that 50 per cent of cases of papillary tumor of the [illegible] ureteral or bladder implants

In the absence of such definite evidence of a tendency for [illegible]ment in tumors of the renal parenchyma, it has never been thought [illegible] apply this principle to tumors of this type However, Deming[3] did [illegible] that complete ureterectomy be carried out in all cases of renal [illegible] papillomatous characteristics, whether cortical or pelvic

THEORIES ADVANCED FOR METASTASIS TO THE LOWER URINARY [illegible] SIMILAR TUMORS IN THE KIDNEY

Implants to the surface of the ureter and bladder McDonald[4] [illegible] demonstrated cells of papillary and parenchymal tumors in the [illegible]gested their diagnostic value Green[5] and Hovenanian and D[illegible] planted viable tumor cells from one species to another and it [illegible] to believe that these cells could be implanted in the same [illegible] continuous, similar, mucous membrane

Willis,[7] who is quoted by most authors in discussions of the [illegible] gives strong support to this theory of implantation, in his [illegible]ported by Boger[8] in 1928 He states. "At autopsy on a man [illegible]

Read at annual meeting, American Urological Association, New York, [illegible] 1954

[1] McDonald, J R and Priestley, J T, J Urol, 51: 245, 1944

[2] Caulk, J R Tr Am A Genito Urin Surg, 30: 50, 62, 1927

[3] Deming, C L J Urol, 69: 1, 1953

[4] McDonald, J R Urol Seminar, American Urological Association [illegible]

[5] Green, H S, J Exp Med, 73: 475, 1941

[6] Hovenanian, M S and Deming, C L Surg Gynec and Obst [illegible]

[7] Willis, R A Spread of Tumors in the Human Body Lo[illegible] 1934

[8] Boger, A Beitr z path Anat u z allg Path, 80: 640, 1928

previously been removed for carcinoma, the left ureter, as it entered the true pelvis, was found embedded in a mass of growth and its walls were invaded. The small hydronephrotic left kidney exhibited tumor masses occupying the calyces and extending out into the renal parenchyma. The part of the ureter intervening between the point of invasion and the kidney was free of growth and this was confirmed microscopically. There were no metastases in any other viscera. Histological study of the original rectal growth, of the invaded ureter and of the tumors of the kidney disclosed adenocarcinoma of similar character in all situations.

"Boger excluded haemic metastases as the origin of the renal deposits on the grounds that there were no other visceral metastases; that the opposite kidney was not affected and that none of the tumors in the affected kidney were cortical in situation. He also excluded retrograde, lymphatic or venous spread up the ureter to the kidney because there was no microscopic evidence of this.

"Boger concluded that his case was one of ascending urinogenous metastases facilitated by the ureteral obstruction and urinary stasis. His thorough and succinct account leaves little room for doubt of the correctness of his interpretation.

"This case is of special significance regarding the whole question of urinogenous metastases. If an extrinsic tumor, such as a rectal adenocarcinoma, is capable of invading the urinary passages and yielding implants in these passages, the same capacity in a much higher degree must be acceded to the tumors indigenous in the urinary passages themselves."

Extension by lymphatics of the ureter. Parker,[9] who has done a large amount of work upon the lymphatics, states that "Over one hundred separate injections of various portions of the wall of the ureters indicate that no complete network of lymphatic channels may be demonstrated throughout the wall of the ureter by means of Gerota's injection mass" and "the lymphatic capillaries in the walls of the ureters give rise to lymph collectors which pass diagonally outward through the musculature of the ureter."

The conception that bacteria in ascending infections are more easily transported through the lymphatics than the lumen of the ureter is apparently based upon the conclusions of Bauereisen.[10] Parker does not believe that his experimental work substantiated such conclusion but rather confirmed the diagonal course of the lymphatics through the wall of the ureter.

Kimbel and Ferris,[11] referred to by McDonald and Priestley, believed that the later involvement of the outer coats of the ureters suggested that these tumors did not spread by the lymphatics.

Willis notes that papillary tumors rarely invade the lymphatics and if so, there should be widespread lymphatic extension in the adjacent structures which are not seen in the implants.

Manifestation of disease of the mucosa of the entire urinary tract. Ewing,[12] John-

[9] Parker, A. E.: J. Urol. **43:** 811, 1940.

[10] Bauereisen, A.: Quoted by Parker.

[11] Kimball, F. N. and Ferris, H. W., J. Urol., **31:** 257–304, 1934.

[12] Ewing, J.: Neoplastic Diseases, 3rd ed. Philadelphia: W. B. Saunders Co., 1928, p. 127.

son,[13] Caulk and others believed that there was evidence that these ureteral and bladder tumors were a part of a disease process involving this transitional cell type of mucous membrane. The aniline dye tumors of the bladder and the multiple papillomatous tumors would lend credence to the possibility of some such factor. Colby[14] states that this theory is strengthened by the fact that in 1.2 per cent of cases of carcinoma of the renal pelvis, the pelvis of the other kidney is involved.

The development of papillary tumors in the bladder, long after removal of the kidney, the ureter and adjacent bladder, would suggest some focus similar to that in the kidney or ureter above.

Willis, previously referred to, had certain objections to this view. He believed that pre-existing inflammatory process, probably required for such development, is rarely present and if these growths were independent formations, they should be found bilaterally more frequently and not appear to occur in every case in the ureter of the involved kidney. He also dismisses the conception of the secretion of some substance exciting neoplastic growth in the tract below as being fantastic.

Metastases from kidney tumors. These have been found in all organs and could be the basis for the secondary lesions in the ureter and bladder. The bladder as a site of metastases has been reported and we have had a case of melanotic sarcoma involving the bladder from a primary lesion in the axilla. Willis, in his textbook discussion of blood borne metastases to the bladder, mentions several cases of bladder involvement from distant melanotic lesions and as in our case, the bladder lesions were superficial, in the mucous membrane and rarely invaded the muscular coat. In this regard, he considered the case of renal parenchymal tumor with similar metastases in the bladder as reported by Suzuki,[15] in 1909, as a possible retrograde venous embolism following the occlusion of the renal vein.

Garrett and Mertz[16] refer to their report of metastases to the bladder in a case of Wilms tumor of the kidney and Melicow[17] mentions Lattes' case with a similar metastasis. In the former case, the occurrence of the bladder lesion about the ureteral orifice of the involved side and later evidence of lower quadrant mass would suggest the possibility of implant rather than blood borne metastases in this case.

Presman and Ehrlich[18] in a review of metastatic tumors of the ureter found 37 cases reported, mostly from the stomach and prostate, eight of each, and none from the kidney. McCrea and Peale[19] in another review in 1951, adding four cases to the series, two of their own, believe that such metastases occur more frequently than suspected and suggested examination of the ureters in all cases of tumors with metastases. They found no ureteral metastases from the kidney. Klinger[20] reviewed 5000 autopsies at the Henry Ford Hospital to the year 1948, and selected for study cases of urinary tract involvement by metastatic malignant growths. Compression or direct involvement were not considered. Lymphomas provided the greatest number of primary lesions and bilateral renal involvement was frequently found.

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[13] Johnson, F. P. Northwest Med., 38: 236–240, 1939.
[14] Colby, F. H. Essential Urology, 2nd ed., Baltimore: Williams and Wilkins Co., 1953.
[15] Suzuki, S. Berl. klin. Woch., 46: 294, 1909.
[16] Garrett, R. A. and Mertz, H. O. J. Urol., 70: 694–703, 1953.
[17] Melicow, M. M. Personal communications, 1953, 1954.
[18] Presman, D. A. and Ehrlich, L. J. Urol., 59: 312–325, 1948.
[19] McCrea, L. E. and Peale, A. R. Urol. and Cutan. Rev., 55: 1–11, 1951.
[20] Klinger, M. E. J. Urol., 65: 114, 1951.

The rarity of reported cases of metastatic involvement of the ureter and bladder from tumors of the kidney would also seem to make implantation the more probable route. However, Melicow in his personal communication, after reviewing the pathological slides in our two cases, agrees with the diagnosis, but from his study believes that we are dealing with vascular metastases rather than implants. His records in the Department of Urology of Columbia University contain no similar cases.

A review of the literature upon this subject indicates that conclusive evidence of the manner in which the lower tract is involved is lacking. It would appear probable, however, that metastases by implantation does frequently occur in the urinary tract in papillary lesions and possibly with other types of renal tumors.

In the more recent urological literature, James P. Macalpine[21] must be given credit for bringing our attention to the fact that implants from clear cell carcinoma do occur. In reporting his case, Macalpine reviewed the literature and gave quotations from the monographs of several authors. Most of these discussions appear to have referred to direct extension of tumor even to the bladder. Macalpine believed that these references, for the most part, were vague, without pathological reports and he thought probably concerned papillary pelvic tumors.

Suzuki,[15] in 1909, found a bladder implant from a tumor of the renal parenchyma and Szymonowicz,[22] in 1932, reported involvement of the bladder and urethra following a so-called hypernephroid tumor. Hovenanian,[23] in 1950, reported a case of ureteral implantation of clear cell carcinoma of the kidney and referred to Macalpine's series. Mertz, Howell and Hendricks,[24] in 1941, added another to the thirteen reported cases.

Hugh Young,[25] in *Young's Practice of Urology*, mentions, without case report, the possibility of the extension of parenchmyal tumors to the bladder without involvement of the ureteral wall. In referring to the difficulty in the classification of such malignant kidney tumors, Young called attention to the presence, in some cases, of papillary formations and their tendency to invade, simulating papillary pelvic tumors. Stoerk, mentioned by Young, suggested the following sequence of events in the formation of so-called hypernephroma: contracted kidney, cyst formation, papillary cystadenoma and hypernephroma. With papillary formations in parenchymal tumors implantation can be more easily explained. It would seem, however, that if this were the usual occurrence, in the formation of these tumors, we should frequently see the various stages, rather than the end result.

With the evidence that we have lower tract involvement, no matter how accomplished, measures to prevent such involvement at surgery, as well as a consideration of their possible presence in hematuria would appear justified. It would not seem necessary, with the few reported cases, to perform ureterectomy in all parenchymal tumors except for those of papillomatous nature, as suggested by Deming. However, early and low ligation of the ureter, as well as the renal pedicle, may prevent manual expression of tumor cells into the ureter and bladder during mobilization of the kidney. Hematuria after nephrectomy without ureterectomy for papillary tumor of the renal pelvis draws attention immediately to the bladder and ureter. Such postoperative bleeding in parenchymal tumors also should bring to our mind the possibility of implants or metastases to the bladder, ureteral stump or urethra.

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[21] Macalpine, J. B.: Brit. J. Surg., **35:** 113, 1948.

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[23] Hovenanian, M. S.: J. Urol., **64:** 188, 1950.

[24] Howell, R. D., Hendricks, J. W. and Mertz, H. O.: J. Urol., **46:** 1103, 1941.

[25] Young, H. H. and Davis, D. M., Young's Practice of Urology. Baltimore: W. B. Saunders Co., p. 506, 1926.

CASE REPORTS

Case 1. P. A., a butcher aged 66, was admitted September 20, 1952 (Albany Hospital No. 53957). He complained of blood in the urine of 2 days' duration. General examination was negative. Urinalysis revealed red blood cells. X-ray study of the urinary graet was negative. Excretory urography showed a filling defect in the middle and lower calyces of the left kidney; the right kidney was normal. An x-ray of the chest was negative. Cystoscopic examination revealed normal bladder mucosa. Urine recovered from the bladder was clear but microscopic study disclosed red blood cells. Urine from both kidneys was clear. Left retrograde pyelography disclosed a filling defect. Impression: Parenchymal renal tumor, left. A left nephrectomy was performed after rib resection. No local or venous involvement was noted. The ureter was ligated in its mid portion. Convalescence was uneventful except for bladder symptoms and blood in the urine, thought to be prostatic in origin.

Pathological report: The specimen was a left kidney that weighed 280 gm. Irregular enlargement was present in the lower pole. On section, an irregular mass was found, 7 cm. in diameter, moderately firm, yellow orange in color with projections of firm, white and translucent material focally hemorrhagic but not necrotic. Tumor had completely replaced lower half of the kidney. The remaining kidney tissue appeared normal. The pelvis was smooth, glistening and normal. The renal capsule and ureter were normal. The diagnosis after microscopic examination was clear cell carcinoma of the kidney (fig. 1).

The patient slowly regained strength. Blood in the urine occurred at times. Cystoscopy showed a suspicious flat lesion to the left of the midline in the dome of the bladder; it did not appear to be the usual bladder tumor. Cystoscopy repeated under spinal anesthesia showed a lesion in the dome of bladder that was removed by a resectoscope. The biopsy was reported as clear cell carcinoma of the bladder (fig. 2). The patient had no further bleeding, and the urine became clear. Left ureterogram (stump of ureter) showed no evidence of tumor. Cystoscopy 3 months later revealed a normal bladder.

Case 2. P. K. B., a man aged 76 (Albany Hospital No. B-49205) gave a history of hematuria. Transurethral prostatic resection had been performed elsewhere 2 years ago for relief of obstructive symptoms. Dysuria, thought to be due to urethral stricture, continued and was temporarily relieved by passage of urethral sounds.

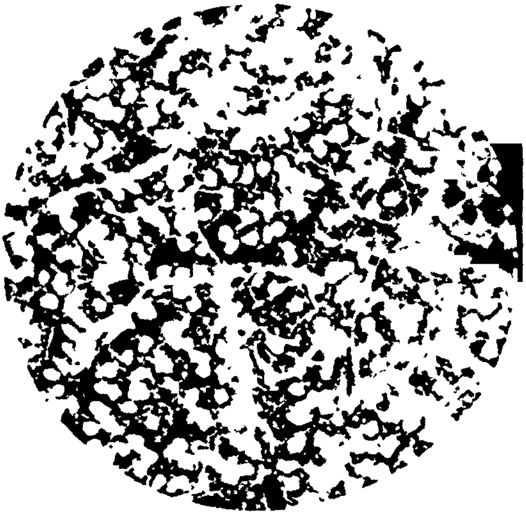

FIG. 1. Case 1. Clear cell carcinoma of kidney

FIG. 2. Case 2. Clear cell carcinoma of bladder

In February 1953, he came under our observation with obstructive symptoms. Cystoscopy revealed considerable prostatic tissue remaining at the vesical neck. A routine x-ray was negative but no excretory urograms were made. X-ray of the chest was negative.

Transurethral removal of 52 gm. tissue, that showed adenocarcinoma, relieved his symptoms until July 1953, when he presented hematuria. Although recurrent carcinoma at the area of transurethral resection was suspected, cystoscopic examination revealed blood jetting from the right ureteral orifice. Ureterogram was suggestive of tumor in lower portion. Nephro-ureterectomy was performed on July 17, 1953. The immediate convalescence was excellent, but 9 months later the patient was losing weight, a mass was palpable through the rectum and the prognosis was poor.

Pathological report: The specimen was a kidney with ureter and lymph nodes and fibro-adipose tissue. Two discrete and similar masses measured 1 ml. in the greatest dimension; they were yellowish in color and fairly friable. Examination revealed a small clear cell carcinoma of the kidney with implants to pelvis, the lower ureter and involvement of aortic lymph nodes. A small papillary cystadenoma was found on the external surface of the kidney. Several pinpoint, yellowish dots and cysts, the largest 1 ml. in diameter, were noted on the kidney surface.

On the side wall of a pyramid one saw the same size and type of lesion, more brownish in color. The cortices and pelves were greatly dilated. Ureter: 17 cm. from the pelvis extending for about 8 cm., yellow, focally hemorrhagic growths,

Fig. 3 Case 2 Clear cell carcinoma of kidney

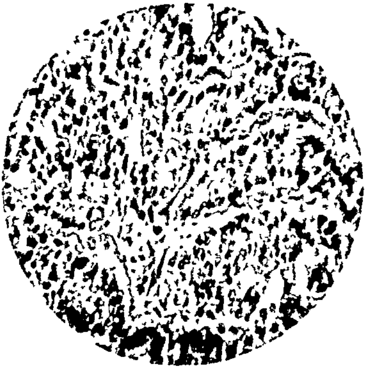

Fig. 4. Case 2. Clear cell carcinoma of ureter

largest 1.8 cm. to 0.5 cm., were seen growing from the wall of the ureter. The remainder of the ureter was normal. The lymph nodes, the largest 2.5 by 1.3 by 1.3 cm., were yellow gray, almost caseous but moderately firm to touch, and focally hemorrhagic. The perirenal tissue revealed no nodes. Diagnosis: Small clear cell carcinoma of kidney with metastases or implants to pelvis, lower ureter and lymph nodes; papillary cystadenoma of kidney (figs. 3 and 4).

SUMMARY

Two cases of involvement of the lower urinary tract from clear cell tumors of the renal parenchyma are reported.

The literature is reviewed and considered theories of such involvement discussed.

Possibility of these lesions should be considered in the pre- and postoperative studies of cases of parenchymal tumors.

Early ligation of the ureter, as well as the renal pedicle in all cortical tumors, with possible ureterectomy in certain types, may be indicated.

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OBSERVATIONS ON HEALING OF URETERAL MUSCLE: RELATIONSHIP TO INTUBATED URETEROTOMY

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In 1950 the senior author performed the Davis type of ureterotomy[1] upon a patient with a right hydronephrosis due to stricture of the ureter just below the ureteropelvic junction. Eventually removal of the right kidney was necessary. At time of nephrectomy the ureter, at the site of previous incision, was completely stenosed. In view of the total failure of the initial procedure, it was decided to re-investigate the problem of regeneration of ureteral muscle and attempt to determine factors involved in failure of the operation.

PART I

Methods and materials. A total of 20 dogs (male and female) was used in the first portion of the study. The animals were anesthetized with intravenous and intraperitoneal sodium pentobarbital. After adequate anesthesia had been obtained, the flank area was prepared aseptically and draped. Either the right or left kidney and corresponding upper one-third of the ureter were then exposed and a nephrectomy performed. A segment of ureter, measuring 20 mm. in length and 4 mm. in width, was then excised; the proximal end of the resected segment was 2 cm. from the proximal end of the ureter. The portions of the ureter above and below the resected area were in continuity with each other through the remaining segment of ureter whose width was usually about one-third of the original circumference of the ureter (fig. 1, *A*). The ureter was intubated then with a hollow No. 18 gauge polythene tube for a distance of 8 cm. The polythene tube was kept in position in the ureter by suturing the proximal end of the ureter to the proximal end of the tube and the distal end of the tube to the adjacent ureter. The proximal and distal limits of the resected portion of the ureter were marked, for future identification, with fine black cotton sutures taken through the serosa and muscularis (fig. 1, *B*).

In 10 dogs the intubated ureter was replaced in its original retroperitoneal position without any further procedures, but in the remaining 10 animals, the intubated ureters were wrapped first in retroperitoneal fat and then replaced. A Penrose drain was left inlying in the retroperitoneal space and the wound closed. Usually the drain was removed four to five days postoperatively. Autopsies were performed upon the animals at desired postoperative intervals. Some animals were sacrificed at 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, and 14 weeks, postoperatively. At necropsy the ureter and peri-ureteral tissue were

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* Present address: 4705 Montrose Boulevard, Houston, Texas

Read at annual meeting, American Urological Association, New York, N. Y., May 31, 1954

[1] Davis, D. M., Strong, G. H. and Drake, W. M.: Intubated ureterotomy: Experimental work and clinical results. J. Urol., 59: 851-862, 1948

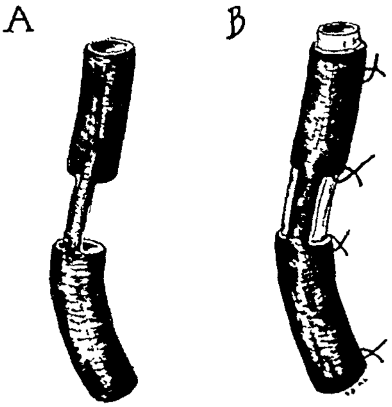

FIG. 1. *A*, partially resected ureter. *B*, intubation of partially resected ureter. Note sutures fixing tube to ureter and sutures marking longitudinal limits of resection.

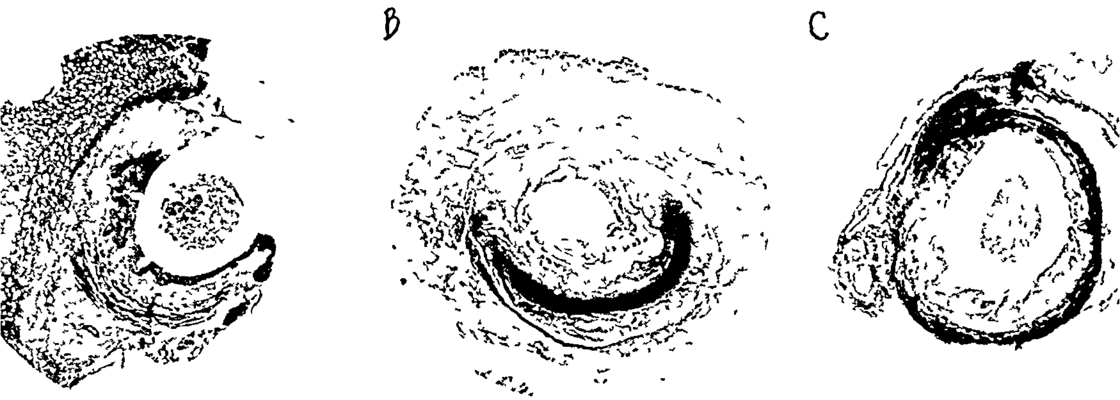

FIG. 2. Sections of intubated resected ureters stained with Gomori trichrome and phosphotungstic acid hematoxylin. *A*, ureter intubated 2 weeks. *B*, ureter intubated 4 weeks. *C*, ureter intubated 6 weeks.

examined grossly and then the intubated ureter was removed and placed immediately in Zenker's fixing solution. Paraffin sections obtained from the resected portion of ureter were stained with hematoxylin-eosin, Gomori trichrome and phosphotungstic acid hematoxylin. The latter two methods differentiate clearly between muscle and connective tissue.

Results. Microscopic examination of the ureters revealed complete regeneration of the mucosa by the end of the third week. The defects in the ureters were not bridged by smooth muscle until the sixth postoperative week. Most of the ureters intubated for six weeks or more demonstrated a small amount of residual fibrous tissue in the muscle and serosal layers. Figure 2 depicts the microscopic appearance of the resected intubated ureters; figure 2, *A* is the ureter intubated for 2 weeks; figure 2, *B* 4 weeks; and figure 2, *C* 6 weeks after partial resection. *Observe the small amount of muscularis in the 2-week section as compared with the 6-week section.*

It was noted during postmortem gross examination that the intubated ureters *not covered with fat* were angulated and rigidly fixed to the underlying psoas muscle by dense fibrous adhesions. In fact, a large amount of fibrous tissue usually surrounded the ureter, making it quite difficult to dissect. These findings were not present when the intubated ureters had been enclosed in fat.

PART II

Methods and materials. Six dogs were used in this section of the study. After adequate anesthesia and preparation a kidney and its corresponding upper one-third of the ureter were exposed. A segment of ureter 20 by 4 mm. was resected in the manner described in Part I, nephrectomy was not performed.

Urinary drainage of the kidney and intubation of the ureter were accomplished with the use of one hollow No. 18 gauge polythene tube. The tube was made long enough to extend from 7 cm. below the distal end of the resected portion of the ureter up through the ureter, pelvis and parenchyma of the kidney to 4 cm. beyond the skin. Multiple perforations were made in that portion of the tube which would be lying in the pelvis of the kidney for urinary diversion (fig. 3). The combination nephrostomy-intubation polythene tubing was then placed in position in the ureter and kidney, and the ureter enclosed in fat. A Penrose drain was placed in the retroperitoneal space and the wound closed.

After 6 weeks of intubation the polythene tubing was removed. The dogs were autopsied at intervals ranging from 6 weeks to 3 months after discontinuation of intubation. The ureters were tested for patency and ureteral tissue obtained for microscopic examination.

In one dog the splinting tube was removed 2 weeks postoperative by the animal. The dog was "posted" 6 weeks later.

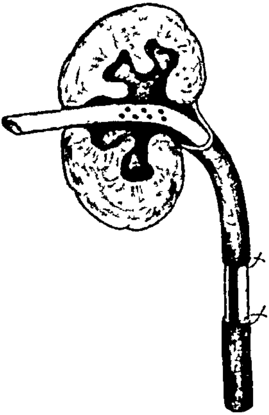

FIG. 3. Partially resected ureter intubated with polythene tubing which functions as splint and nephrostomy.

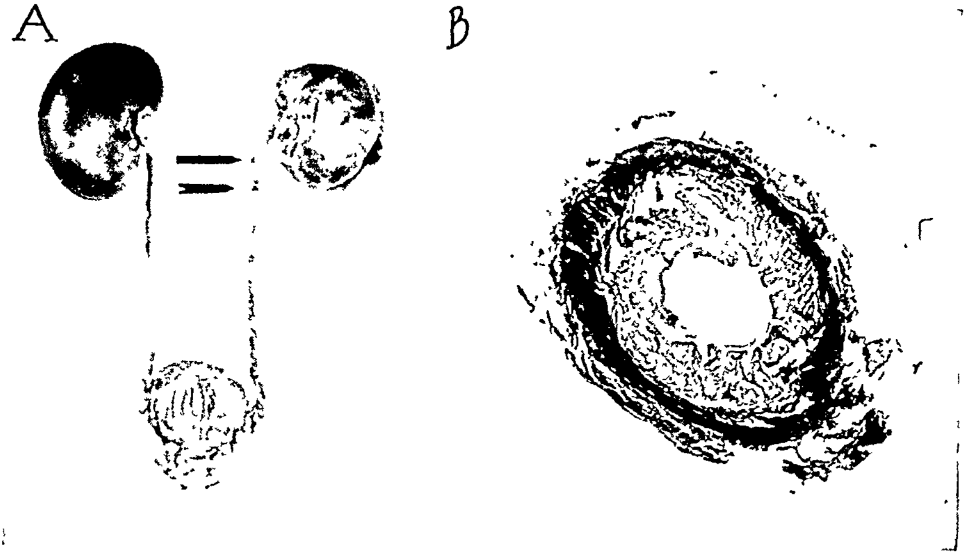

FIG. 4. *A*, gross appearance of intubated, partially resected ureter 3 months after polythene tubing was removed. Segment of ureter demarcated by arrows was portion originally resected. *B*, section from segment of ureter.

Results. The ureters were entirely patent and the resected portion almost completely bridged by muscle in the animals that had been intubated for 6 weeks. Figure 4, *A* illustrates the kidneys, ureters and bladder of one of the experimental animals; the segment of ureter demarcated by the arrows was the portion originally partially resected. The microscopic section of the operated segment of the ureter is depicted in figure 4, *B*. Observe the extent of the muscular layer! All of the kidneys on the operated side demonstrated varying degrees of pyelonephritis but no hydronephrosis with the exception of the animal whose tube was removed in 2 weeks. At autopsy this dog's ureter was completely stenosed at the site of resection and a tremendous hydro-ureter and hydronephrosis were present above the area of stricture.

PART III

Methods and materials. Only two animals were used in this portion of the study. After exposing a kidney and the corresponding upper one-half of the ureter in the usual manner, a piece of cellophane was wrapped around the ureter for a distance of 20 mm. The flank wound was closed and the dog allowed to convalesce for 6 weeks. At that time the dog was reoperated and observation disclosed (in both dogs) stricture of the ureter at the site of cellophane wrapping with hydro-ureter and hydronephrosis above the stricture. The cellophane was removed from around the ureter and the strictured portion incised in a longitudinal manner. A No. 18 gauge polythene tube was then placed in position through the kidney and ureter for purposes of intubation and urinary diversion as described in Part II; the ureter was enclosed in retroperitoneal fat. The polythene tube was removed 6 weeks after operation. The dogs were followed for a period of two more months and then sacrificed. Gross and microscopic examination of the ureter and kidney were carried out.

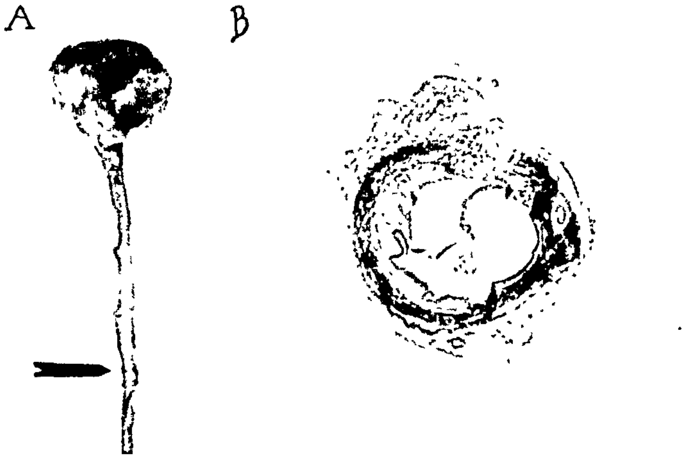

FIG. 5. *A*, gross appearance of cellophane-strictured ureter after incision and intubation. *B*, section from incised segment.

Results. Gross examination at necropsy disclosed normal caliber of the ureter throughout, in both dogs. The hydro-ureter and hydronephrosis had disappeared (fig. 5, *A*). Microscopic examination of the incised portion of the ureteral stricture disclosed complete encirclement with muscle (fig. 5, *B*).

DISCUSSION

Berry, in an article written in 1920,[2] stated that "the present conception of the healing and regeneration of smooth muscle is somewhat vague and leaves much to be desired"; this statement still holds true at the present time. Little research has been conducted in the field of smooth muscle regeneration during the last thirty years.

The evidence obtained in our study suggests strongly that ureteral smooth muscle regenerates and to a marked degree. It should be emphasized, however, that the evidence is controvertible. It is possible for the ureteral defect to be bridged in two ways: 1) by regeneration of smooth muscle or 2) by stretching and hypertrophy of the smooth muscle in the narrow bridge of ureter remaining after excision. That the second proposal is not an impossible feat can be comprehended readily if one thinks of the tremendous dilatation normal ureters undergo in certain disease states. A definite answer will be had when histochemists have developed a method for distinguishing between old and regenerated smooth muscle.

Whatever the process by which the ureter heals, there can be no controversy regarding the reformation of a patent lumen with the use of the Davis intubation technique—provided certain precautions are taken. The experimental findings indicate that peri-ureteral fibrosis is the most important factor in the failure of the Davis procedure. This complication can be avoided partially by enclosing the incised portion of the ureter in retroperitoneal fat and by preventing prolonged leakage of urine into the operative area. If the narrowing of the ureter is due primarily to peri-ureteral fibrosis, it will be necessary to dissect the ureter free from the fibrous tissue before intubation and enclosure in fat are performed. Merely incising the ureter and intubating it will result in failure; this circumstance was responsible for the poor result in the case which stimulated the present study.

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[2] Berry, F. R The regeneration of smooth muscle cells. J. Med. Research, 41: 365-372, 1920

If large defects in the ureter are to be bridged, it is imperative that the splinting tube remain in place for at least 6 weeks. The experimental data indicate that 6 weeks are required for complete enclosure of the ureter by muscle although only 3 weeks are necessary for regeneration of the mucosal layer. It is probable that the shorter periods of intubation will suffice for smaller ureteral defects.

In accordance with Davis' concepts, it is believed that the splinting tube should be of as large a caliber as can be accommodated by the normal portion of the ureter.

CONCLUSIONS

It is probable that ureteral smooth muscle is capable of significant regeneration.

Recurrence of ureteral narrowing after intubated ureterotomy is due primarily to peri-ureteral fibrosis. This can be obviated by enclosing the intubated ureter in fat and by avoiding leakage of urine into the operative site.

The authors are highly indebted to Alice Hatt Lapides for the illustrations in this paper.

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URETERAL REGENERATION IN DOGS: AN EXPERIMENTAL STUDY BEARING ON THE DAVIS INTUBATED URETEROTOMY

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The intubated ureterotomy has become a standard procedure in the armamentarium of the urologist since it was first described by David M. Davis[1, 2] in 1943. It solves the perplexing problem of bridging a tissue gap in the ureter, and hence derives its chief value.

The remarkable property of the ureter to close its own defect, like less highly specialized tissues, is of great interest to the urologist. The present study has for its purpose a closer histologic examination of the tissue which bridges the ureteral defect, particularly with reference to the fate of the muscularis, in the hope of reaching a better understanding of the process biologically and clinically.

TECHNIQUE

Stock mongrel dogs of both sexes were anesthetized with intravenous nembutal and operated on under aseptic surgical technique. Intravenous fluids and antibiotics were used when indicated by the animal's condition to ensure its survival. The procedure was performed through a flank incision in the first group of 7 dogs, through a transperitoneal approach with no effort made at reperitonealization in the second group of 4 dogs. A nephrectomy was done in the first group of animals and not in the second.

In this procedure, the ureter was freed from its bed and incised longitudinally. A polyethylene catheter, size 4 to 7F, was passed into the ureter and anchored several centimeters away from the experimental field by a silk suture through the ureter and catheter. A "window" was excised from the ureteral wall over the catheter for lengths of 0.5 cm. up to 2.0 cm. From 30 per cent to 60 per cent of the circumference of the ureter was removed. The limits of the "window" were marked by a nonabsorbable suture through the peri-ureteral fat or serosa. No attempt was made to re-approximate the edges of the ureter. The regions of the ureter above and below the experimental area were also splinted to ensure security of the splint and to serve as control tissue for study. The upper ureter was used in the first group, the middle ureter in the second group. The ureter was replaced along its natural course as closely as the partially flexible polyethylene tube would allow. The abdominal wound was closed according to standard surgical technique.

The animals were sacrificed from 23 days to 162 days later by an overdosage of

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Read at annual meeting, American Urological Association, New York, N. Y., May 31, 1954.

[1] Davis, D. M.: Intubated ureterotomy. A new operation for ureteral and ureteropelvic stricture. Surg., Gynec. & Obst., 76: 513, 1943.

[2] Davis, D. M., Strong, G. H. and Drake, W. M.: Intubated ureterotomy, experimental work and clinical results. J. Urol., 59: 851, 1948.

intravenous nembutal. The kidneys and ureters were dissected free, examined grossly and fixed in 10 per cent formalin in saline. Too close dissection of the ureter, which might have resulted in trauma, was avoided in order to preserve the tissues for microscopic study. The splint was not removed until autopsy.

After fixation, selected sections were cut, dehydrated and embedded in paraffin. Hematoxylin and eosin stains, Masson's trichrome and Verhoeff van Gieson's stains were used routinely in this study.[3] A few of the ureters were studied by serial skip sections in order to be sure no pathologic change over the length of the ureter was missed.

No animals were discarded from the series except on the basis of loss or premature death. Minor details of technique were refined and changed in succeeding experiments as experience was gained with the methods used.

RESULTS

Gross findings. Every ureter treated according to the above-described method re-established gross tubular continuity around the splint. The site of the ureteral "window" could not always be distinguished grossly at autopsy from the ureter above or below it. In contrast to this, the ureteral segment which had been splinted stood out clearly by virtue of its marked hypertrophy and thickening. Grossly the changes attributable to repair were barely noticeable in contrast to the changes attributable to prolonged splinting.[4]

In several instances it was obvious that a longitudinal contracture of the ureter had occurred in the region of the ureter from which a "window" had been excised. In one instance, the two marking sutures were found to be in juxtaposition even though the original defect had been 2 cm. long.

Peri-ureteral adhesions of varying density were noted at autopsy. Some of these were dense enough to suggest possible interference with motility through the involved segment. In the second series of animals, in which a transperitoneal approach was used, the omentum or other organs were occasionally adherent to the ureter.

True calculus formation was not encountered.

Microscopic findings. The most significant finding in each dog was the re-establishment of the integrity of the ureteral tube around the splint. In 2 dogs the ureteral mucosa formed a tube beside the splint. Another lumen, in the nature of a false passage, was formed beside this by serosa or muscularis to include the tube.

The ureteral wall showed no line of demarcation between the original and the reconstituted segments. Only with the aid of an external mark could the "window" be located with assurance.

The epithelium showed a complete and rapid regeneration covering the defect. There were evidences of epithelial ingrowths and buds in the muscularis and submucosa in far greater number than are normally encountered. This has been

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[3] Gridley, Mary Francis, Comp.: Laboratory Manual of Special Staining Technics, Armed Forces Institute of Pathology, 1953.

[4] Cordonnier, J. J. and Roane, J. S.: Ureteral splinting: An experimental evaluation of prolonged ureteral splinting. Surg. Clin. N. Amer., 30: 1523, 1950.

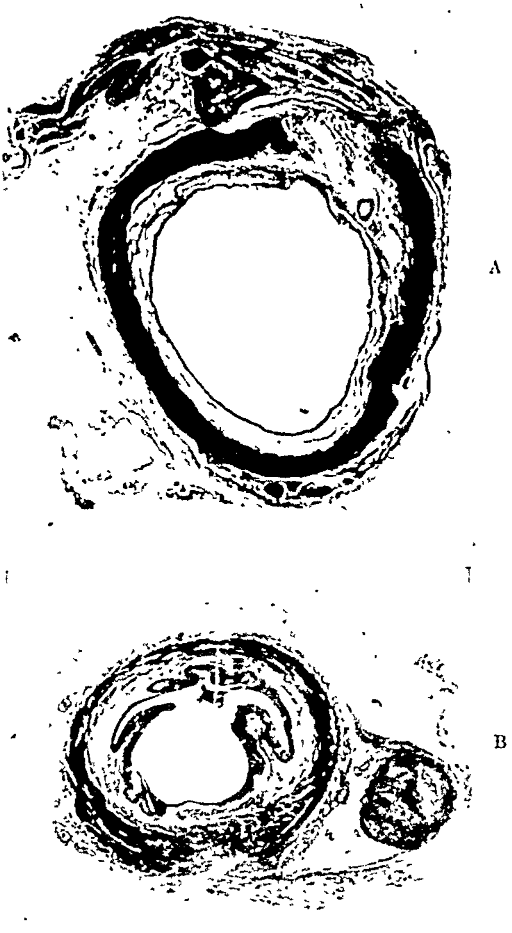

FIG. 1. *A*, good result. *B*, compare with result after longitudinal ureterotomy alone.

previously noted by Marion[5] and Hryntschak.[6] In juxtaposition to these epithelial buds and cysts would be seen, on occasion, islets of bone.[7] Papillary epi-

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[5] Marion, Henri. Étude critiques et expérimentales des plaies transversales de l'uretère. J. d'urol. 27: 273 and 369, 1929.

[6] Hryntschak, T.: Zur Histologie und Physiologie des querdurchtrennten Harnleiters. Ztschr. f. urol Chir. u. Gynak., 42: 268, 1936.

[7] Huggins, C B The formation of bone under the influence of epithelium of the urinary tract Arch Surg , 22: 377, 1931.

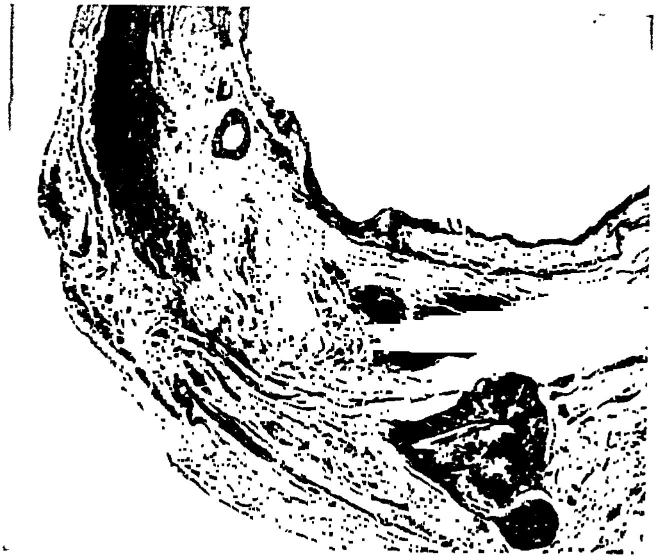

FIG. 2. Higher magnification of "window" which originally had been a 50 per cent defect in circumference. Notice break in muscularis at site of lesion, submucosal epithelial cyst and serosal suture and adhesion.

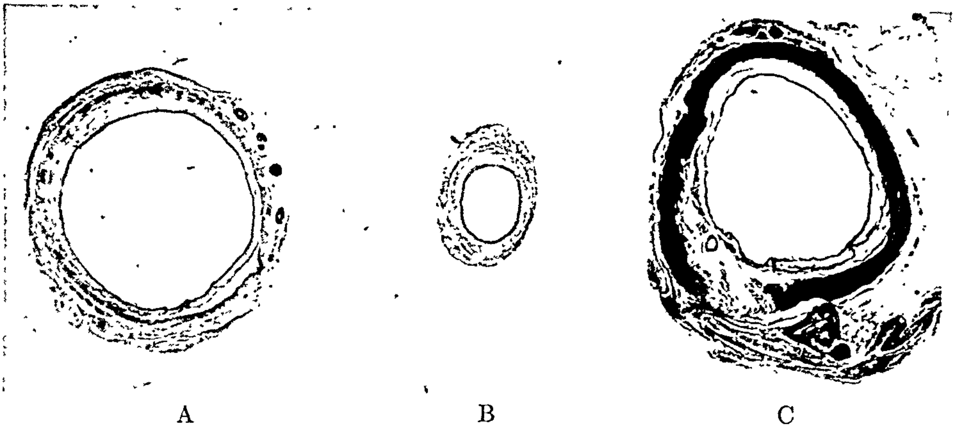

FIG. 3. Comparison of sizes of splinted, unoperated ureter, *A*; unsplinted, unoperated ureter, *B*; and splinted, operated ureter, *C*. All are from same dog.

thelial projections were seen in the lumina on occasion in association with inflammatory exudates in the muscularis or under the mucosa.

The area of structural change often involved less than 20 per cent of the circumference and less than the length of the original defect created experimentally. A goodly portion of the original defect had been closed by "normal ureteral wall."

The muscularis of the regenerated area was seen to be changed considerably from normal in architecture. However, the area of change here was much smaller than the area of the original "window." Much of the bulk of this layer consisted of fibrous tissue rather than muscle bundles. Those muscle fibers which were present were not arranged in their usual orderly circular and longitudinal layers, but seemed to lie in a completely chance arrangement. Entire radial segments of the ureteral muscular layer were seen to be replaced by scar tissue.

Changes in the serosa microscopically confirmed the gross findings of periureteral adhesions, occasionally to surrounding organs Inflammatory exudates in the serosa and submucosa were present but not prominent

The effect of the serosal silk or cotton marking suture was noted as a small typical foreign-body granuloma in the serosa. The effect of the ureteral splint *per se* was a marked increase in size of the ureter and hypertrophy of the muscularis This has been previously described by Cordonnier and Roane [4]

SUMMARY OF PROTOCOLS

Dogs No. 4 through 18 were subjected to nephrectomy in order to remove the urine from the field of study. In dogs No 19 through 25 the urinary stream was diverted only by the indwelling catheter used as a splint In the first series, 7 dogs and 1 control are included They were autopsied from 23 to 162 days after the operation In the second series, 4 dogs and 1 control are included. They were autopsied from 24 to 133 days after the operation See table 1

(The remaining dogs are not included in this report for diverse reasons—premature death, loss, equivocal location of the "window" at autopsy, etc. The incomplete data from these dogs supported the reported conclusions; their elimination merely simplifies the discussion.)

Dog No 4. At operation a defect 1½ cm long was made over a 7F polyethylene catheter, removing 50 per cent of the circumference of the ureter

Autopsy 162 days later showed the ureter to be enlarged, thickened and indurated in its splinted portion. The peri-ureteral adhesions were easily dissected free The splint was in the position expected Grossly no defect was

TABLE 1

Dog No	Window Size (cm)	% Circumference Ureter Removed	No of Days Growth	Catheter Size (French)	Ureteral Hypertrophy	False Passage	Muscular Scarring	Muscular Disorganization	Muscular Epithelial Islands	Muscular Bone Islands	Muscular Inflammation
4	1.5	50	162	7	✓		✓	✓		✓	
6	1.0	50	143	4	✓		✓	✓	✓		
7	No incision		108								✓
9	1.0	40	129	5	✓	✓					✓
11	0.5	50	75	6	✓		✓	✓	✓	✓	✓
12	0.5	30	69	?	✓						
13	0.5	50	95	6	✓		✓	✓	✓		
18	2.0	60	23	4	✓	✓	✓				
	1.0	40			✓		✓				
19	2.0	50	80	4	✓		✓	✓	✓		✓
21	2.0	40	132	4	✓		✓	✓	✓		
22	2.0	50	125	4	✓			✓	✓	✓	✓
25	Longitudinal incision		24	4	✓			✓			

apparent in the ureteral wall, though on longitudinal section, the wall was thickened for three-fourths of its circumference at one point.

Microscopic study at the site of the lesion showed an interruption of the muscularis with dislocation and disruption of the normal pattern of the fibers by scar tissue. The outer layer of muscular fibers seemed to be uninterrupted at some points. Foreign body granulomas were seen only in relation to the sutures, but bone formation was evident submucosally.

Dog No. 6. Dog 6 was autopsied 143 days after excision of a 1 cm. "window" which had removed 50 per cent of the circumference of the ureter over a French polyethylene catheter. The ureter was enlarged, thickened and entangled in many adhesions. On longitudinal section, the ureteral mucosa was smooth and uniform with slight narrowing at the level of the "window."

Microscopically, many mucosal pouches were seen. The muscularis was scarred and slightly disorganized; one area showed myxomatous or young connective tissue as an interruption to its usual structure.

Dog No. 7. This dog was subjected to nephrectomy and ureteral isolation, but no intubation of the ureter and no excision of tissue were done. Autopsy 108 days later showed the ureter to be adherent, but of the same size and mass as the opposite ureter.

Microscopic examination of the ureter showed normal architecture with chronic inflammation. Search of the sections showed one interruption of the muscularis with no apparent overlying mucosal change; this may have been an artefact or a point where blood vessels entered the arterial wall.

This dog served as a control to eliminate the effect of nephrectomy and operative trauma as a possible cause of the observed changes in the preceding animals.

Dog No. 9. Dog 9 was autopsied 129 days after operation, when 35 per cent of the circumference had been excised for 1 cm. over a 5F catheter. The ureter was enlarged and embedded in adhesions.

Microscopic examination showed marked inflammatory changes in the wall of the ureter with moderate scarring and muscular disorganization. Closure of muscularis around the splint, but closure of the mucosa without inclusion of the splint, had resulted in formation of a "false passage."

Dog No. 11. Dog 11 was autopsied 75 days after operation, at which time a "window" 0.5 cm. by 50 per cent of the circumference had been excised. Microscopic section showed disorganization, inflammation and a mucosal outpouching which completely interrupted the muscularis. In one area bone formation was seen in relation to a mucosal outpouching.

Dog No. 12. In dog 12 only 30 per cent of the ureteral circumference was removed for 0.5 cm. Autopsy 69 days later showed the ureter to be densely adherent and hypertrophied in the splinted portion.

Microscopic examination showed an amazing recovery with mucosal changes to localize the area of injury, but no muscular break. The cut ends of musculature had been apposed perfectly and structural continuity had been restored.

Dog No. 13. Dog 13 was autopsied 95 days after creation of a "window" 0.5 cm. by 50 per cent of the circumference over a 6 French catheter. Microscopic examination showed interruption of the muscularis at the site of the old "window" by scar tissue and submucosal epithelial inclusion cysts. Also seen was the effect of a serosal suture which was well localized as a foreign body granuloma confined to the serosa. Special connective tissue stains showed muscle bundles coursing through the scar tissue.

Dog No. 18. Dog 18 was autopsied 23 days after two intubated ureterotomies were done in the right mid-ureter. The upper one resulted in removal of 2 cm. of ureteral wall over a 60 per cent circumference, the lower of 1 cm. for 40 per cent. A 4F polyethylene splint was used. At autopsy the ureter had closed grossly. The experimental areas seemed to be slightly whiter and less thick.

The upper lesion showed closure without inclusion of the splint so that a double lumen or "false passage" was formed. There was no evidence of muscularis, but merely fibrous tissue around the splint. The lower lesion closed around the splint, but again, a goodly portion of the muscularis had been replaced by fibrous tissue.

Dog No. 19. Dog 19 was operated on transperitoneally. The right ureter was splinted by a 4F polyethylene catheter, but no nephrectomy was done. A "window" was cut in the mid-ureter 2 cm. long removing 50 per cent of the circumference of the ureter. At autopsy 80 days later, the ureter was seen to be shortened in the region of the serosal marking sutures so that the two sutures which were 1 cm. apart at operation were found to be in juxtaposition at autopsy.

Microscopic examination showed marked distortion of the structure of the wall of the ureter at the site of the lesion and a break in the muscularis. There were slight inflammatory changes and some interposition of epithelial nests in the muscularis layer.

Dog No. 21. Dog 21 was operated on similarly and showed similar microscopic findings after 132 days.

Dog No. 22. Dog 22 was operated on similarly and showed gross contraction of the region of the lesion at autopsy; microscopically the ureteral wall showed marked distortion with epithelial and bony inclusions in the muscularis layer.

Dog No. 25. In dog 25 the left ureter was incised longitudinally and splinted by a 4F polyethylene catheter. No "window" was excised. Microscopically a break in the muscularis due to fibrosis was seen at the site of the incision, but no distortion of architecture, bony or epithelial inclusions.[11]

REVIEW OF LITERATURE

Davis's[1, 2] original experiments in dogs showed the muscularis layer of the ureter growing around its circumference over a period of 6 weeks to close the gap in the ureter. However, no mention was made of differential stains to separate connective tissue fibers from muscle bundles in the muscularis or to study the internal arrangement of these bundles. In his studies, he noted osseous formation in a few instances submucosally.

[11] Karns, Z and Perlmann, S Klinische und experimentelle Studien über die Heilung der Nierenbecken- und Harnleiterwunden Ztschr f Urol , 21: 659, 1927.

Kimbrough and his co-workers[8] confirmed that in dogs the ureter closed successfully around a splint after longitudinal incision. However, the healed ureter showed gross and microscopic evidence of fibrosis of varying degree at the site of closure. Osseous formation was noted in the ureter of one dog after 10 weeks splinting; muscle hypertrophy was noted in the others.

Hryntschak[6] studied ureteral repair in the transected ureter in dogs. He described a classical sequence of wound healing with subsequent scar formation. He noted evidence of later invasion of the scar by muscular fibers from either side, but never re-establishment of normal architecture. He found no evidence of true regeneration of muscularis.

Wiseman[9] found that the transected ureter, which had been re-approximated loosely over a rubber catheter, closed successfully, but with thickening at the site of closure. This thickening was found, upon microscopic study, to be due to an increase of fibrous tissue with diffuse round cell infiltration.

Needham[10] describes wound healing in smooth muscle as a process of compensatory hypertrophy of the remaining muscle. It is well known that epithelial layers grow over a defect rapidly from all sides.

SUMMARY

The histologic nature of the ureter reconstituted after excision of a "window" and healing over an indwelling catheter was studied with routine and connective tissue stains.

Findings on 11 dogs are reported; the ureteral "windows" varied from 0.5 cm. to 2.0 cm. in length with removal of 30–60 per cent of the ureteral circumference and were marked externally by a serosal, nonabsorbable suture. Dogs were autopsied from 23 to 162 days after operation.

Grossly the ureter had closed completely with minimal thickening or induration at the site of the "window." Peri-ureteral adhesions were frequent.

Microscopically, two false passages were formed by closure of the ureter with exclusion of the splint. The "window" had shrunk slightly in length and moderately in circumference, due to closure on its periphery by ureteral wall indistinguishable from the surrounding wall. Centrally, the epithelium had regenerated, but the muscularis showed a varying degree of replacement fibrosis with disorganization of the arrangement of the remaining muscle bundles. Occasional ectopic epithelial nests, associated at times with bone formation, were seen in this region of the muscularis, too. However, in many instances reconstitution of the ureteral wall had been complete except for a radial scar in the muscularis no larger than was seen after healing from a linear ureterotomy, and in one instance it was well-nigh perfect. The serosa showed evidence of peri-ureteral adhesions and occasional chronic inflammatory exudates.

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[8] Kimbrough, J. C., Furst, Y. N., Worgan, D. K. and Denslow, J. C.: Intubated ureterotomy; report of animal experimentation and clinical cases. J. Urol., 64: 74, 1950.

[9] Wiseman, J. L.: Observations on the stimulating influence of temporary rubber splinting on regeneration following ureteral resection: An experimental study. Brit. J. Urol., 6: 11, 1934.

[10] Needham, A. E.: Regeneration and wound-healing. Methuen's Monograph on Biological Subjects. New York: John Wiley & Sons, Inc., 1952.

Whether true regeneration of the muscularis at the periphery of the "window" had occurred or whether scar contraction centrally had caused spreading and hypertrophy of the adjacent wall cannot be concluded from our data.

Hypertrophy of the muscular and connective tissue elements of the ureteral wall subsequent to prolonged indwelling catheterization was noted in all dogs.

Prolonged splinting is followed by hypertrophy of the ureter, and possibly encourages scar formation in the ureter.

Acknowledgment is made to Dr. Alex W. Boone, Jr. for making available many laboratory facilities; to Dr. E. P. Alyea for suggesting the problem and for guidance; to Dr. George Margolis and Dr. John E. Dees for several valuable suggestions; and to Mr. Ben Britt, Mr.Philip Pickett and Mr. John W. Pittman for technical help.

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POTASSIUM DEFICIENCY SYNDROME FOLLOWING BILATERAL URETEROSIGMOIDOSTOMY

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Bilateral ureterosigmoidostomy involves a severe derangement of the lower urinary tract. It is thus not surprising that a number of complications and sequelae may follow this procedure. Although it is true that operative mortality and immediate postoperative complications have decreased, the late results are still not satisfactory. By improving operative procedures one has attempted to prevent the usual and well-known late sequelae such as urinary stasis, reflux and urinary tract infections. More recently interest has been focused upon the electrolyte disturbances, which are manifested usually as hyperchloremic acidosis with azotemia and rarely as hypopotassemia. Ferris and Odel (1950) in a series of 141 cases of ureterosigmoidostomy observed hyperchloremic acidosis with varying degree of azotemia in 79 per cent of their cases. No mention was made of hypopotassemia in this study or in most other reports on the electrolyte disturbances following bilateral ureterosigmoidostomy. However, Foster, Drew and Wiss (1950) observed the combination of hyperchloremic acidosis and hypopotassemia. A case of hypopotassemia with complete flaccid quadriplegia was reported by Diefenbach, Fisk and Gilson (1951). This complication seems to be very rare. Probably other cases have been encountered, although not recorded in the medical literature.

The present communication deals with another case of potassium deficiency and flaccid paralysis which developed 14 months after total cystectomy and bilateral ureterosigmoidostomy.

CASE REPORT

A 38-year-old clerk was admitted to the hospital on May 7, 1951 with the chief complaint of rapidly progressing weakness of arms and legs of 6 hours duration.

The past history revealed that he had been in good health until March 1948 when a seminoma of the left testis was removed. Postoperatively he received x-ray treatment. In March 1949 the patient had macroscopic hematuria. At cystoscopy it was observed that the major part of the bladder wall was covered by tumor masses. This tumor was suspected to be metastases from the seminoma, removed one year previously. X-ray therapy was therefore instituted. The hematuria disappeared. Surgery was considered inadvisable as the x-ray picture of the pelvis suggested the presence of bone metastases. He remained asymptomatic, however. A repeated x-ray examination of the pelvis in November 1949 showed that the previously demonstrated translucency had disappeared. A repeated cystoscopy showed the same tumor masses in the bladder. A biopsy

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was reported as a papilloma, suspected of malignancy. No metastases were demonstrated. An excretory urogram was normal. The nonprotein nitrogen was about 35 mg. per cent. Operative treatment was decided on. On January 31, 1950 right ureterosigmoidostomy was performed *ad modum* Coffey I and on March 22, 1950 cystectomy and ureterosigmoidostomy on the left side was done *ad modum* Nesbit. Pathological diagnosis was a benign papilloma. Postoperatively the patient did well. In August 1950 the patient had acute pyelitis which responded well to antibiotics. He continued rather well and was able to handle his work as a clerk, although he felt somewhat more tired than before his illness started. His bowel movements were regular. There was no diarrhea. In the middle of April 1951 he began to feel more tired.

Following an excretory urogram on May 7, 1951 he felt dizzy and nauseated for a few minutes He had no rash. Similar reactions had previously been observed after excretory urography. Five hours later he noticed gradually increasing weakness, first in the arms and somewhat later in the legs. Within a couple of hours he was *not able to move his arms and he could not* walk. He was immediately admitted to the hospital. There was no change in the caloric intake which was adequate. He had suffered no vomiting The patient had not noticed any increase of the urinary output though he had felt somewhat more thirsty during the two preceding weeks. The family history was negative.

The physical examination revealed a rather healthy looking man. There was no disorientation. The *temperature* was 38C, *the pulse rate* was 90, *the blood* pressure was 150/80. The lungs and the heart were normal to percussion and auscultation. The abdomen was slightly distended, nontender and showed the operative scars. The patient exhibited a flaccid quadriplegia. Small movements in the shoulders and hips could be carried out. No gross bodily movements were possible. He was unable to sit up but he could raise his head. Examination of the cranial nerves was negative. There was no dysphagia. No sensory changes were observed The deep tendon reflexes were normal. Abdominal and cremasteric reflexes were present. There were no Babinski and Chovstek signs.

The excretory urogram demonstrated on the right side a slight dilatation of the ureter, the renal pelvis and the calyces. On the left side the pyelogram was normal The concentration of the dye in the kidneys was within normal limits. Laboratory examination revealed a nonprotein nitrogen of 67 mg per cent, a CO_2 content of 10 mEq/L and a serum potassium of 2 3 mEq/L. The serum calcium was 10.2 mg. per cent and the blood sugar was 160 mg. per cent. An electrocardiogram demonstrated changes suggestive of hypopotassemia with depression of the S-T segments, depressed and broadened T-waves and prolonged Q-T-interval (fig. 1).

The patient was treated with 2000 ml. of 1 3 per cent sodium bicarbonate containing 2.67 g of potassium chloride and 0.75 g of potassium orthophosphate intravenously. He also received fruit juices and meat broth. Within a few hours a dramatic improvement occurred. He became able to raise his arms and legs and within 12 hours he was able to walk. The electrocardiogram improved but did still show changes of hypopotassemia despite the fact that the serum potas-

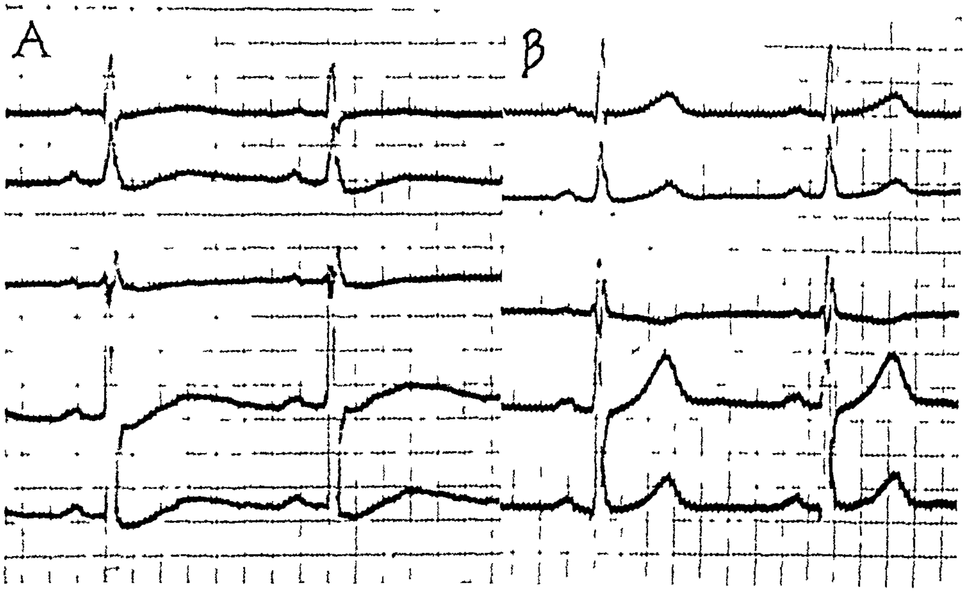

FIG. 1. *A*, electrocardiogram during hypopotassemia. *B*, after correction of electrolyte disturbance.

TABLE 1. *Laboratory data*

Date	NPN	CO_2-content	Chlorides	Sodium	Potassium	Calcium	Hemoglobin	Red cell count	White cell count
	mg %	*mEq/L*	*mEq/L*	*mEq/L*	*mEq/L*	*mg %*	*gm /100 ml*		
1/4 1950	34	27					12.1	3.6	
7/5 1951	67	10	103	143	2.3	10.2	13.3	4.0	9200
8/5 1951	51	22			3.6				
11/5 1951	46	32			3.9	9.4			
17/5 1952	35	24	107	151	5.0		12.6	4.0	8200
27/6 1953	43	21	100	145	4.9	10.7	12.8	4.3	6300

sium had increased to 3.6 mEq/L. The CO_2 content increased to 34 mEq/L. Within a few days the electrocardiogram was completely normalized (fig. 1) and the serum potassium remained normal. The nonprotein nitrogen decreased to 39 mg per cent.

The patient has then been observed for 2 years. He has suffered from at least four attacks of pyelitis which have responded well to streptomycin. There has been no clinical or laboratory evidence of hypopotassemia. Potassium has been administered intermittently. The patient has been able to carry out his work. The laboratory data are summarized in table 1.

DISCUSSION

The very rapid development of flaccid quadriplegia without other neurologic manifestations suggested a diagnosis of familial periodic paralysis, but the family history was negative. In view of the previous history of bilateral ureterosigmoidostomy it was logical to look for a connection between the present clinical picture and a renal disturbance. The diagnosis of hypopotassemia was strongly supported by the electrocardiographic changes and finally established by the low concentration of potassium in the blood serum Further proof of the diagnosis was obtained from the dramatic response to the administration of potassium Although there are no pathognomonic symptoms and signs of potassium deficiency the clinical findings in this patient were highly suggestive

Hypopotassemia in renal insufficiency is well known (Brown, Currens and Marchand, 1944, and others), and has been studied a great deal during recent years It is considered that this type of hypopotassemia is due to renal tubular damage although the details of the mechanism have not been elucidated so far

The mechanism by which hypopotassemia developed in this patient is not clear but the following explanation may be offered Secondary to the ureterosigmoidostomy the patient experienced episodes of ascending urinary infections and a slight urinary stasis resulting in renal tubular damage with concomitant inability to produce acid urine and unsatisfactory synthesis of ammonium This led to a depletion of the base, particularly of sodium and potassium In order to spare sodium an increased amount of potassium was excreted Thus the patient probably had a low serum potassium although not low enough to produce clinical hypopotassemia When the excretory urogram was made the tubular re absorption of potassium probably was blocked by the tubular excretion of the organic iodine compound This additional loss of potassium resulted in the clinical syndrome observed in this patient There is no reason to assume that iodine hypersensitivity, if present, would have caused the actual syndrome

It may be argued that this patient suffered from hyperchloremic acidosis described by Ferris and Odel as a common complication to bilateral ureterosigmoidostomy The patient, however, did not show the clinical picture of hyperchloremic acidosis, nor was hyperchloremia present

It should be observed that the muscular weakness had completely disappeared when the serum potassium had increased to 3 6 mEq/L At this time electrocardiographic changes suggestive of hypopotassemia were still present In the case reported by Diefenbach, Fisk and Gilson the abnormal electrical findings had disappeared completely at a serum potassium concentration of 2 46 mEq/L Probably there is no close parallelism between the electrocardiographic changes and the concentration of potassium in the blood serum It has been discussed a great deal whether the electrocardiographic changes are due to extracellular or intracellular potassium deficiency This problem is still unsolved We believe that the determination of the serum potassium concentration is the most useful chemical aid in the evaluation of potassium deficiency This determination gives an indication of the state of extracellular potassium but does not necessarily reflect the state of cellular stores of the ion

This case is presented to call the attention to hypopotassemia as a complication to bilateral ureterosigmoidostomy Judged from the scantiness of reports in the literature it probably is a rare complication However, less dramatic cases than the present one may have been overlooked The present observations may also be of significance in the discussion of the advisability of excretory urography in patients with renal tubular damage

SUMMARY

A report is given of a patient who presented an acute flaccid quadriplegia due to hypopotassemia following total cystectomy and bilateral ureterosigmoidostomy and possibly provoked by excretory urography.

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FIVE YEARS' EXPERIENCE WITH URETERO-ENTEROSTOMY BY THE 'COMBINED' TECHNIQUE

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In this country and probably throughout the world, urinary diversion operations of one sort or another are being done with much more frequency. This is to some extent a reflection of the extended surgical effort in the treatment of cancer of the pelvic organs but also is a result of attention being directed critically to diversion operations themselves in an effort to improve the immediate and long term results. This paper cites in detail our own immediate and available late results following uretero-enterostomy performed by the Coffey 1 and 'combined' techniques in the hope that the information disclosed will be of help in evaluating uretero-enterostomy as a method of urinary diversion and perhaps clarify our thoughts relative to the comparative values of this operation, ureterostomy, nephrostomy, construction of cecal pouch, and ileal loop procedures.

Until 1950 the senior author's experience with uretero-enterostomy was confined principally to the Coffey 1 operation. On the basis of its use in 25 cases, mostly in association with cystectomy for cancer of the bladder, certain deductions may be drawn. The overall uretero-enterostomy-cystectomy mortality, which I shall not attempt to separate, was 2 cases (8 per cent). Though the mortality was acceptable, complications both early and late from uretero-enterostomy were numerous and disturbing. Eight of the surviving 23 patients have ended up with ureterostomy or nephrostomy due to stricture developing at the site of anastomosis. In one case urinary calculi developed necessitating surgery. At least 20 of the 41 ureters transplanted to the bowel became strictured to such a degree that moderate to severe hydronephrosis developed in the affected kidney.

On the other hand, 9 of the 23 surviving patients have done quite well. Thirteen of the 23 are still living from 6 to 8 years after operation. One patient died from common duct surgery after an extremely satisfactory convalescence from combined uretero-enterostomy and cystectomy. Nine patients died from residual cancer within about one year, 1 died after 3 years and one, 5 years from residual cancer. Uretero-enterostomy did not contribute to death in any case.

Several conclusions are permissible from a study of these cases: 1) In spite of the numerous complications, the operation was valuable. Its use should be continued and the technique improved, if possible, to reduce complications. 2) Patients need not die from the complications of uretero-enterostomy if they are carefully followed and drainage of the upper urinary tract instituted promptly when necessary. 3) General health has been good after operation considering age and condition of the patients. 4) The chief difficulty has been stricture developing at the site of anastomosis with the bowel.

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In searching for the cause of stricture at the site of anastomosis the following factors seem to have played roles of varying importance: preoperative radiation therapy, poor bowel preparation, spillage of intestinal contents at operation, excessive freeing of the ureter, inadequate incision of the bowel in forming the submucous trough, too tight closure of the bowel muscle flaps forming the roof of the tunnel. One or more of these probably contributed to the difficulty in each case, but in spite of due consideration to these factors, as we become aware of them, and the best possible technical performance of the operation, stricture and hydronephrosis continued to develop in some cases. Autopsy studies indicated that generally obstruction (stricture) developed at the tip of the ureter in the bowel lumen rather than in the tunnel. It appeared that such an outcome might be unavoidable when a segment of ureter was allowed to protrude into the bowel lumen where it invariably became infected and contracted. This same observation must have prompted Nesbit[1] to develop his 'direct elliptical connection' technique and Cordonnier[2] his 'end to side direct anastomosis'.

Experience with Nesbit's operation and the evaluation of others led to the early recognition of the fact that, although stricture at the site of anastomosis was less likely, gas and even fecal material frequently refluxed to the renal pelves with resulting pyelonephritis and deterioration of kidney function. The published results of Cordonnier's[3] operation indicate that results are quite good but that reflux of gas occasionally occurs.

In an effort to preserve the good points of these direct anastomosis techniques and at the same time develop a method which might prevent reflux, the senior author began in 1950 to perform an operation which combined the direct elliptical anastomosis of Nesbit with the tunnel utilized by Coffey. Early results were very encouraging so that this technique and results obtained up to that time were presented before the 1951 meeting of American Association of Genito-Urinary Surgeons.

At the same time, animal experimental work was carried out to test, in dogs, the comparative results obtainable from the various operations developed for uretero-enterostomy advocated and practiced in different quarters.[4] A simultaneous and independent similar study was being conducted by Weyrauch and Young.[5] These two studies demonstrated that in dogs the 'combined, direct anastomosis tunnel' technique gave the best results. Furthermore, we again demonstrated that the correct formation of a submucous tunnel does in fact establish a valve which prevents reflux of gas and fecal contents from the bowel to the ureter.

With these facts to encourage us we have continued using this technique which has been modified somewhat.

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TECHNIQUE

Preparation of the bowel is routine and takes 3 days. Catharsis is induced by castor oil. A low residue, high protein diet is given. Streptomycin, 0.5 gm. 4 times a day by mouth, has been used to render the large bowel bacterial count as low as possible, though other drugs may be used as effectively. Enemas are given each evening and the morning of operation, taking pains to have the patient empty the bowel as completely as possible. After anesthesia is established the lower bowel is thoroughly lavaged through a long, soft rectal tube until washings are clear.

Operation is carried out usually under intratracheal general anesthesia. When exploration and uretero-enterostomy alone is to be done, a long midline incision is preferred. If cystectomy is to be done also, a modified Cherny incision may be used.

After exploration the table is tipped so that the patient is in moderate Trendelenburg position and the small bowel packed off with pads. The sigmoid is inspected and freed from adhesions from its beginning in the descending colon to the rectosigmoid (fig. 1, *A*).

If either ureter is dilated, the dilated one is approached first so that it may be divided and allowed to drain while the opposite ureter is being freed, divided and implanted in the bowel. This allows for contraction of a dilated ureteral musculature with decrease in circumference and cross section area and consequent easier transplantation.

The usual procedure (fig. 1, *B*) is to first expose the left ureter through a small incision in the retroperitoneum below the proximal sigmoid at the pelvic brim. It is divided above one clamp placed at this point. The proximal end of the distal stump is ligated. The proximal end, if urine is considered uninfected, is allowed to drain freely after it is tagged with a fine silk stitch. If infected, a soft rubber catheter is threaded up to the pelvis and this allowed to drain outside the drapes. The proximal ureter is freed gently from its bed to a point behind the mesentery of the sigmoid through which a small transverse incision is made. The end of the ureter is pulled through the mesentery, taking pains to be sure that no sharp angulation results (fig. 1, *C* and *D*).

The site chosen for anastomosis between the ureter and the bowel is just at the beginning of the sigmoid after it becomes mobile. The anastomosis is performed through a slightly obliquely placed incision in the anterior taenia, beginning as close to the mesentery border as possible. We have found the more natural course for the ureter from the retroperitoneum to be through the mesentery of the sigmoid. When the anastomosis is performed through the posterior taenia, it is difficult to be sure that the ureter and bowel are properly aligned after replacement of the sigmoid and that accurate measurement of the ureter for length is not possible. This brings up the question of redundancy and angulation of the ureter, both possible causes of obstruction

The ureter, after carefully measuring it for proper length without tension, is prepared by incising the inferior lip of the cut end for a distance of 5–7 mm. and

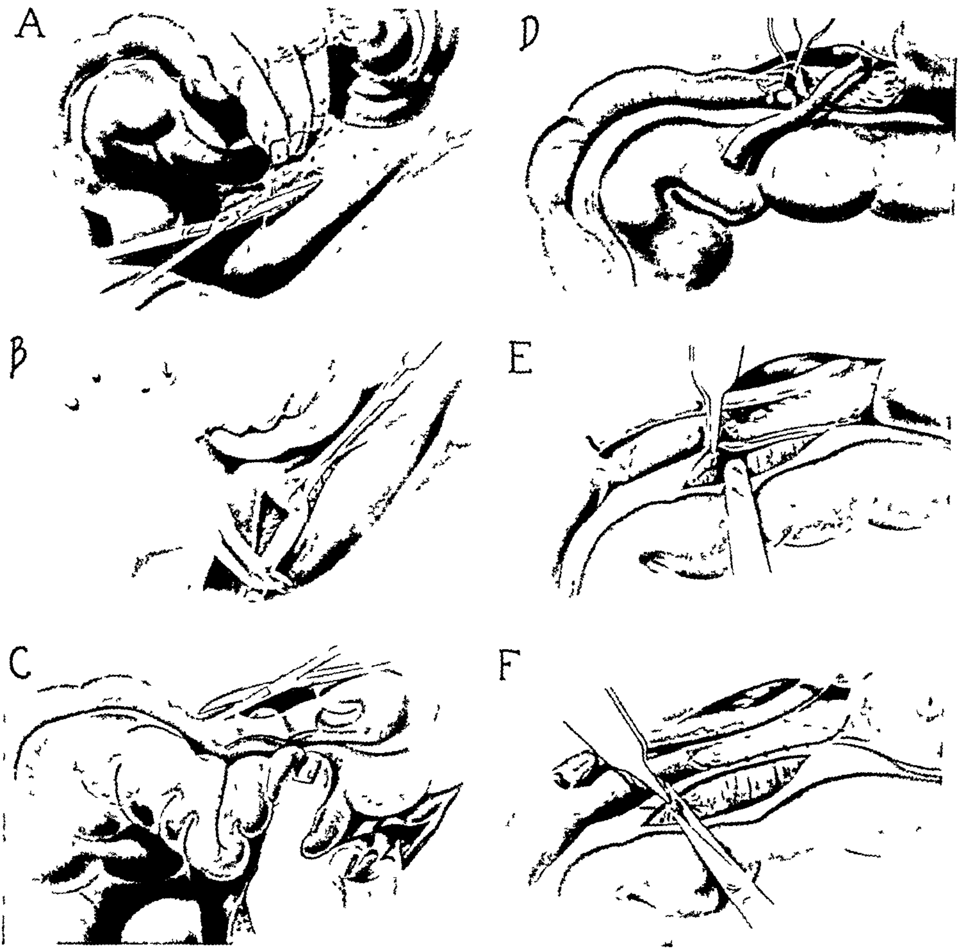

Fig. 1. *A*, sigmoid mobilized from left pelvis. *B*, ureter freed and transected; proximal end allowed to drain freely, and distal stump ligated. *C*, transverse incision made in mesosigmoid over finger behind sigmoid; ureter mobilized by blunt dissection to point just above incision in mesentery. *D*, inferior margin of mesosigmoid incision sutured to sigmoid to immobilize bowel and provide loose fatty bed for ureter. *E*, taenia incised slightly oblique and mucosa separated from flaps of muscularis and muscularis mucosa *F*, bowel stoma is fashioned.

trimming the sharp edges of the ureter to leave an oval elliptical ureteral os considerably larger in cross section area than the transversely severed ureter (fig. 2, *A*).

At the point in the sigmoid opposite or adjacent to the site of incision in its mesentery, through which the ureter is drawn, the peritoneum forming the lower margin of the mesentery incision is sutured to the mesenteric margin of the sigmoid by a row of fine interrupted silk sutures to turn down the peritoneum and form a loose connective tissue bed for the ureter as it passes to the bowel (fig. 1, *D*). The trough in the bowel is then made by incising the anterior taenia for a distance of 2.5–3 cm. diagonally toward the point where the ureter will emerge from the retroperitoneum. The incision (fig. 1, *E*) in the bowel wall must be carried down to the mucosa itself. This may be accomplished by incising the various layers of the bowel wall at the distal end of the trough until the mucosal

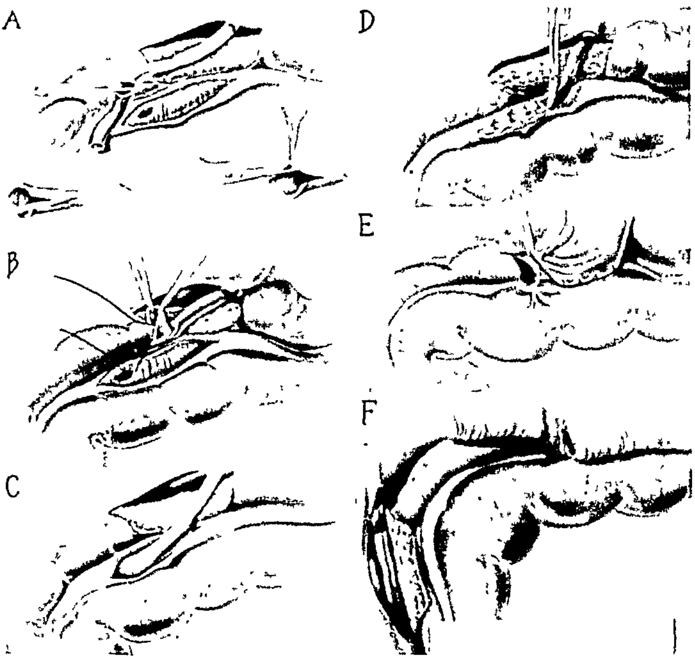

Fig. 2. *A*, ureter measured and its end fashioned obliquely as an ellipse. *B*, anastomosis constructed between full thickness of ureteral wall and bowel mucosa using interrupted 00000 chromic catgut sutures. First stitch taken at apex of ureteral ellipse and at proximal point of bowel stoma. *C*, end to side anastomosis complete. *D*, submucosal tunnel for ureter made by closing muscle flaps loosely over ureter avoiding constriction of ureter as it enters tunnel. *E*, *upper margin of mesosigmoid incision is tacked to bowel over anastomosis and* tunnel to retroperitonealize anastomosis.

layer is identified, sometimes by actually perforating it. Having done this, one may dissect back along the trough within the proper layer and create flaps of musculature on either side of the incision by gently stripping the mucosa from the overlying muscularis. To do this one should use delicate plastic forceps and scissors. When it is done properly the bowel mucosa easily invaginates into the lumen so that when the ureter is placed in the trough and the muscle flaps loosely sutured over it, the ureter lies in the bowel wall as in a hammock without being compressed at all.

A small circular opening in the mucosa of the bowel at the distal end of the trough is made by picking up the mucosa and snipping out a small circular piece with tiny curved scissors (fig. 1, *F*). A direct anastomosis between the prepared end of the ureter and the bowel mucosa is done, using interrupted sutures of 5–0 chromic catgut (fig. 2, *B* and *C*). Silk has been used successfully in several cases but in animals we have observed that the sutures sometimes fail to slough out and may act as a foreign body on which calcium salts may be deposited. Usually

10 or 12 sutures are used to make an essentially watertight anastomosis. No further sutures are placed to fix the ureter to the bowel, but the muscular flaps of bowel wall are loosely sutured over the ureter using 3 or 4 sutures of fine silk. Retroperitonealization of the area of anastomosis and fixation of the bowel is accomplished by suturing the superior peritoneal edge of the incision in the sigmoid mesentery over the site of the anastomosis, again using fine silk sutures (fig. 2, *E*).

The right ureter is implanted utilizing the same technique. The site for anastomosis of the right ureter to the bowel is determined by allowing the sigmoid to curve gradually across the midline without any redundancy or angulation to a point where it lies adjacent to the proximal end of the divided right ureter. An important point is good fixation of the bowel to the retroperitoneum so that tension on the ureter is completely avoided. Sutures must be placed to secure the sigmoid to the posterior peritoneum (fig. 2, *F*) between the sites of anastomoses to render the bowel immobile and prevent a small bowel herniation between the sigmoid and the posterior peritoneum. This is important so that not only will small bowel obstruction be unlikely but no tension on the anastomosis will be generated by distended small loops of intestine.

Important points of technique are:

1) Gentle freeing of only enough ureter to allow anastomosis to be done.

2) Proper measuring of ureter in relation to anastomotic site so that neither redundancy nor tension exists.

3) Careful *construction of a trough as outlined, exposing the mucosa of the* bowel.

4) Accurate, tight anastomosis.

5) Loose closure of the trough by a minimum of sutures.

6) Fixation of bowel to prevent tension on the suture line and angulation of ureters.

One difficulty we have encountered in the fashioning of the trough has been the occasional perforation of the mucosa at points away from the distal end of the trough where anastomosis must be done. We have sutured such rents with fine catgut or silk, but we have wondered whether an occasional poor result may not be due to additional reaction or spillage in the trough because of such secondary perforation.

Postoperative care, in general, has been surprisingly simple. A long, soft rubber tube with multiple perforations has been strapped in the rectum and connected to gravity drainage. This tube is frequently irrigated with normal saline to maintain free drainage. Urine is usually draining from the rectal tube by the time the patient returns to his room after operation. A Miller-Abbott tube is usually placed in the stomach and kept on suction until bowel peristalsis is heard, then clamped, and removed as soon as possible. Penicillin and streptomycin are given for 4 days. Intravenous fluids are given as indicated, depending on urinary output and blood chemistry determinations. The rectal tube is usually removed on the fifth postoperative day and patients are mobilized as quickly as possible.

RESULTS

During the past 5 years this uretero-enterostomy technique has been utilized on 45 patients. Forty patients form the basis of our report, however, since one patient has but recently been operated on and four other patients have not been personally followed. None of the 5 patients not included died from operation. Seventy-seven ureters have been transplanted to the sigmoid in 40 patients.

The age and sex of patients are given in table 1. It will be noted that one patient was operated on at the age of 82. This man, with an essentially nonfunctioning right kidney, *made as rapid and satisfactory convalescence as any of the younger* patients. Right kidney function improved and hydronephrosis disappeared.

Therapeutic indications are listed in table 2: cancer of the bladder in 3, cancer of the prostate in 5, cancer of the cervix invading the bladder base in 3, cancers of the bladder and bowel of separate origin in 2, cancer of the bowel invading the bladder base in 1, urinary incontinence in 3 (female child with complete congenital absence of distal trigone and floor of urethra, middle aged woman with incontinence following many attempts at surgical repair, man with incontinence and severe stricture of bladder neck after radical retropubic prostatectomy), interstitial cystitis in 1.

TABLE 1. *Age and sex*

Ages of Patients (40 Cases)	
0-10	1
11-20	0
21-30	0
31-40	1
41-50	8
51-60	10
61-70	14
71-80	5
81-90	1

Sex of Patients (40 Cases)	
Males	25
Females	15

TABLE 2. *Therapeutic indications (40 cases)*

	Cases
Cancer of bladder	23
Cancer of prostate	5
Cancer of cervix	3
Urinary incontinence	3
Cancer of urethra	2
Cancers of bowel and bladder of separate origin	2
Cancer of bowel invading bladder	1
Interstitial cystitis	1

TABLE 3. *Classification of primary operations (40 cases)*

	Cases
Bilateral ureterosigmoidostomy only	
For nonmalignant disease	4
For palliation of pelvic malignancy	8
Unilateral ureterosigmoidostomy, ligation of contralateral ureter (palliation)	2
Bilateral ureterosigmoidostomy, cystectomy, two stage	11
Bilateral ureterosigmoidostomy, cystectomy, one stage	10
Bilateral ureterosigmoidostomy, contralateral nephro-ureterectomy, cystectomy, one stage	1
Bilateral ureterosigmoidostomy, cystectomy, sigmoidectomy, one stage, with or without terminal sigmoidostomy	2
Bilateral ureterosigmoidostomy, pelvic exenteration, one stage	2

A compilation of original surgical procedures utilized is given in table 3. It will be noted that bilateral uretero-enterostomy was performed on 4 patients for nonmalignant disease and as a palliative procedure for pelvic malignancy (bladder, cervix) on 8 patients. Unilateral uretero-enterostomy and ligation of the contralateral ureter was done on 2 patients for palliation of bladder cancer. No leak from the ligated ureters or subsequent trouble developed in the kidneys thus completely obstructed. This procedure is not recommended unless the operator is sure that the upper urinary tract is not infected. Bilateral uretero-enterostomy and radical cystectomy for cancer of the bladder or prostate was performed in two stages on 11 patients and as a one stage procedure on 10 patients. One other patient had a one stage procedure in which uretero-enterostomy was done on one side, contralateral nephro-ureterectomy and radical cystectomy, because of papillary cancer involving bladder, ureter and renal pelvis on one side. One stage bilateral uretero-enterostomy, radical cystectomy and anterior resection of sigmoid were done in 2 patients for cancer of the bowel invading bladder in one case and independent cancers of the bowel and bladder in another. Pelvic exenteration with bilateral uretero-enterostomy into sigmoid colostomy was done twice: once for independent cancers of the bowel and bladder, and again for cancer of the cervix invading bladder and pelvic tissues.

MORTALITY STATISTICS

Mortality statistics are given in tables 4, 5 and 6. It should be noted that many of these operations have been done wholly or in part by the resident staff under senior guidance so that the results must not be interpreted completely as one man's experience but rather as the combined experience of the urological services of the New England Center Hospital and the Boston Veterans Hospital while the senior author was on service at the latter hospital. No attempt has been made to separate the mortality from uretero-enterostomy and cystectomy, except when uretero-enterostomy was done as the only operation. The mortality was 6 patients (15 per cent) which is too high unless one takes into account the poor condition of many individuals operated on.

Two patients died after bilateral uretero-enterostomy, performed on one pa-

TABLE 4. *Hospital mortality (40 cases)*

	Operations	Deaths %	
Ureterosigmoidostomy ..	12	2	
Ureterosigmoidostomy with pelvic cancer surgery, one stage operation	17	3	
Ureterosigmoidostomy with pelvic cancer surgery, two stage operation	11	1	
Overall mortality . . .	40	6	15%

TABLE 5. *Postmortem analysis of 6 hospital deaths*

Ureterosigmoidostomy:
(A) Female, 67. Death at 48 hours from pulmonary emboli.
(B) Male, 74. Wound dehiscence, 5 days; repaired. Death on 7th day from bronchopneumonia.
Ureterosigmoidostomy with pelvic cancer surgery in one stage:
(C) Male, 46. Left retroperitoneal urinary extravasation; left nephrostomy on 7th day. Death from pulmonary emboli on 16th day after primary operation.
(D) Male, 61. Death from pulmonary emboli on 10th day.
(E) Male, 62. Death from pulmonary emboli after 36 hours.
Ureterosigmoidostomy with pelvic cancer surgery in two stages:
(F) Male, 64. Myocardial infarction 18 days after second operation.

TABLE 6. *Causes of death*

	Cases
Pulmonary emboli..	4
Bronchopneumonia	1
Myocardial infarct .	1

tient (table 5, *A*) for palliation of extensive bladder cancer and on the other (table 5, *B*) preliminary to intended radical cystectomy. The first patient was an extremely poor pulmonary risk with severe asthmatic bronchitis who suffered wound dehiscence 5 days after operation and died 2 days after secondary wound closure of respiratory difficulties and bronchopneumonia. The cough undoubtedly contributed to wound separation and that, together with the necessity for a second anesthesia and wound closure, led to deterioration of pulmonary function. Urinary output was excellent at all times and at postmortem examination both anastomoses were found in excellent condition without evidence of leak or stenosis. Experience with wound dehiscence has led us to adopt either careful closure with multiple stay sutures or buried steel wire. The second patient had respiratory difficulties during and after operation which may have been related to curare administration. She seemed better for 36 hours but died suddenly 48 hours after operation. Autopsy showed multiple pulmonary emboli. The uretero-intestinal anastomoses were excellent.

It will be noted that the mortality after the one stage uretero-enterostomy and cystectomy is higher in this series than that after the two stage procedure—17.6

per cent as contrasted with 9 per cent. We believe that this is significant and plan to use the two stage procedure in poorer risk patients.

The 4 deaths after either one or two stage uretero-enterostomy and cystectomy occurred as follows:

A 46 year old man with extensive infiltrating carcinoma of the bladder was in good condition and without significant ureteral dilatation (table 5, *C*). Bilateral uretero-enterostomy and radical cystectomy were carried out without incident. The patient did not do well though urinary output was adequate. A tender mass developed in the left retroperitoneal space which was incised and drained on the seventh postoperative day. The fluid was clear urine without gas or fecal contamination. A left nephrostomy was also done for safety. The patient developed jaundice and lower nephron nephrosis. This was gradually clearing accompanied by increasing urinary output and falling blood urea nitrogen when pulmonary symptoms developed and the patient died suddenly 16 days after the original operation. Postmortem examination revealed a massive pulmonary embolus. Uretero-intestinal anastomoses were in excellent condition. There was no evidence of residual urine in the left retroperitoneum and no intraperitoneal pathological process. Microscopic study of section from the kidneys showed healing tubular degeneration. We are at a loss to account with certainty for the urine leak, but the ureter above the site of anastomosis must have been injured or leak occurred from the anastomosis which subsequently sealed over without residual evidence of same. This was the only patient who died from causes related to uretero-enterostomy.

Two male patients, one with cancer of the prostate and the other with extensive cancer of the bladder and unrelated cancer of the sigmoid died from pulmonary embolization 10 days and 2 days respectively after operation (table 5, *D* and *E*). There was no evidence that uretero-enterostomy was related to death in either case. Case E should have had a staged procedure.

A patient with extensive cancer of the bladder made an extremely satisfactory convalescence from bilateral ureterosigmoidostomy (table 5, *F*). Excretory urograms before cystectomy revealed marked improvement of unilateral hydroureter and hydronephrosis existing prior to operation and a normal contralateral pelvis and ureter. After cystectomy the patient had an episode of intestinal obstruction which was satisfactorily handled by Miller-Abbott tube decompression, and was apparently making a slow but good convalescence when a myocardial infarct developed and he died. Postmortem examination showed excellently healed and functioning uretero-intestinal anastomoses.

In summary, 6 patients died after bilateral uretero-intestinal anastomosis: 4 from pulmonary emboli, 1 from bronchial pneumonia, and 1 from myocardial infarction. A careful analysis of the postoperative periods, supplemented by autopsy findings in four of the cases, indicates that in only 1 case was death in any way directly related to complications of uretero-intestinal anastomosis (case C). In this case the complication had been recognized, treated, and convalescence seemed assured until pulmonary embolism occurred. The occurrence of pulmonary embolism in 4 cases gives cause for reflection. In 2 cases death occurred so soon after operation that the findings at autopsy were unsuspected. One wonders whether caval ligation should be carried out as an integral part of radical pelvic surgery.

EARLY COMPLICATIONS

Early postoperative complication occurred in 14 of the 40 patients (including patients who died). These are listed in table 7. The complications causing death: pulmonary embolism in 4 patients, wound dehiscence and bronchial pneumonia, transient intestinal obstruction and myocardial infarction, each in 1 patient, have been discussed.

Intestinal obstruction. Intestinal obstruction requiring secondary operation developed in 2 patients. The first patient was a woman of 55 with urinary incontinence who was found at operation to have poor bowel preparation. Considerable soiling of the peritoneal cavity occurred. Intestinal obstruction developed and was found to be due to angulation and fixation of a loop of small bowel at the site of right uretero-intestinal anastomosis where a small abscess was found and drained. Subsequently stricture of a troublesome nature developed at the site of each uretero-intestinal anastomosis, a clear cut relationship between cause and effect.

The second patient had pronounced diverticulosis of the sigmoid bowel. Bilateral uretero-enterostomy was performed with difficulty because of the condition of the bowel but recovery after operation was uncomplicated and excretory urograms showed a normal upper urinary tract. After cystectomy the patient manifested signs of large bowel obstruction in the proximal sigmoid and transverse colostomy was necessary. Subsequently a permanent transverse colostomy has been fashioned and the proximal end of the distal bowel has been closed so that the urine is held and passed from the segment of the lower bowel which has been detached at the level of the mid-portion of the transverse colon. There is no absolute proof in this case that large bowel obstruction resulted from diverticulitis since it is possible at the second operation that retraction of the bowel or manipu-

TABLE 7. *Early operative complications (40 cases)*
One or more nonfatal or fatal complications occurred in 14 patients

	Cases
Pulmonary embolism	4
Intestinal obstruction	3
Retroperitoneal urinary extravasation	2
Urinary and fecal fistula	1
Urinary fistula	1
Wound dehiscence	1
Intraperitoneal urinary extravasation	1
Wound abscess	1
Thrombophlebitis	1
Myocardial infarction	1
Acute pyelonephritis	1
Bronchopneumonia	1

lation may have disturbed its position or fixed it in a position which resulted in kinking, but we believe that extensive diverticulosis is a real hazard when uretero-intestinal anastomosis is being done and that probably a history of diverticulitis should be considered a contra-indication to uretero-intestinal anastomosis. This does bring up the question of the effect of liquid feces on diverticulosis and diverticulitis and one wonders if the overall effect would be good or bad.

Leak from site of anastomosis. This occurred in 3 cases one of which was described above as a contributory cause of death. We have no explanation for this. The procedure was carried out by the senior author in a satisfactory manner.

The second case was that of an elderly clergyman with a papillary carcinoma of the bladder which was thought (W. F. L.) to be amenable to suprapubic electrocoagulation and resection. When the bladder was opened one could not with certainty delineate the margins of the tumor and it appeared that anything short of cystectomy was inadvisable. The patient's bowel had not been prepared for uretero-enterostomy but it was decided to go ahead anyway. Bilateral uretero-intestinal anastomosis was done without much contamination of the peritoneum and seemed satisfactory. Cystectomy was also carried out and proved to be the proper procedure inasmuch as study of the specimen revealed invasion of the prostate. After operation antibiotic therapy was given adequately and the patient did well for several days only to develop tenderness and a mass in the right retroperitoneum which was drained. This was followed by persistent fecal stained urine drainage from the wound. A nephro-ureterectomy was subsequently done and the fecal fistula closed by direct surgical attack (listed under early and late secondary operation, tables 8 and 10). The patient thereafter did well in view of a normal left upper urinary tract but subsequently died of liver metastases. This complication was no more than just reward for an error in evaluation and procedure. The complication in this case was retraction of the ureter due to separation of the anastomosis.

The third case of urinary extravasation or leak occurred in a 65 year old man with extensive carcinoma of the bladder and pelvic lymph node metastases. Bilateral uretero-enterostomy was done as a palliative procedure. From the technical standpoint all went well but the day after operation the patient became distended and by the morning of the second day after operation it was apparent

TABLE 8. *Early secondary operations for complications*
One or more secondary operations were required in 7 patients

	Cases
Exploration for intestinal obstruction	2
Secondary closure of wound	2
Drainage of retroperitoneal urinary extravasation	2
Drainage of intraperitoneal urinary extravasation	1
Nephrostomy	1
Ureterostomy	1
Nephrectomy	1
Colostomy	1

TABLE 9. *Late complications (84 cases)*

	Cases
Stricture of ureters of significant degree (results classified as fair or poor below)	6
Postoperative incisional hernia	3
Pyelonephritis	3

TABLE 10. *Late secondary operations*
These were all performed on patient with early complications

	Cases
Nephrostomy (bilateral)	1
Nephrectomy	1
Closure of urinary and fecal fistula	1

that there was intraperitoneal accumulation of urine. The abdomen was reopened, a large volume of clear urine evacuated, the sites of anastomoses inspected and leakage of urine was demonstrated from the tunnel on the right side. However, the anastomoses seemed in good condition otherwise, so that an extraperitoneal drain was placed to the site of leak and the abdomen closed without drainage. The subsequent course was eminently satisfactory and excretory urography a month after operation showed perfectly normal renal pelves and ureters on both sides.

These three instances of leakage from the sites of anastomoses indicate that prompt, effective drainage usually saves the day.

Other minor complications: wound abscess, thrombophlebitis, acute pyelonephritis, each occurred in 3 patients. The patient with pyelonephritis went on to an excellent convalescence and has never had a febrile episode since.

Operations incident to the treatment of early complications are listed in table 8.

LATE COMPLICATIONS

Late complications thus far have been few. Three incisional hernias occurred but have not been repaired. Pyelonephritis has been observed in only 3 patients. One patient, with a poor anatomical result, who died within one year from residual cancer, had several attacks of pyelonephritis controlled by antibiotic therapy. In another patient, who had had previous pyelonephritis, severe acute pyelonephritis developed in one kidney which did not respond to antibiotics and required nephrectomy. This was puzzling inasmuch as excretory urography demonstrated a good anatomical result. The third patient had bilateral pyelonephritis and required bilateral nephrostomy. She is now free from trouble and doing well.

Pyelographic study since operation has revealed hydro-ureter or hydronephrosis of a significant degree in 6 patients which is presumed to be the result of strictures at the site of anastomoses. These are listed in table 11 as fair or frankly poor results and failures.

TABLE 11. *Ultimate clinical result attained after ureterosigmoidostomy (40 cases)*

	Cases
Excellent (upper urinary tract normal)	24
Good (slight but appreciable hydronephrosis on one or both sides)	7
Fair (moderate to severe hydronephrosis on one or both sides into good *renal function*)	3
Poor (frank failures)	3
Death too early to permit roentgen or anatomic evaluation of ureterosigmoidostomy result	3

TABLE 12. *Analysis of state of 67 individual ureters before and after ureterosigmoidostomy (roentgen observations)*

	Cases
Preoperative dilatation due to disease, regressing to normal after operation	10
Normal ureters showing temporary, slight, postoperative dilatation but ultimately returning to normal	9
Ureters normal before operation and remaining normal at all times thereafter	24
Preoperatively normal ureters showing permanent slight but appreciable dilatation after operation ("good" result)	11
Preoperatively normal ureters showing permanent moderate to severe dilatation with good renal function ("fair" result)	4
Preoperatively normal ureters with frank failure of uretero-enterostomy	6
Ureters dilated preoperatively due to disease, with persistent postoperative dilatation (1 good, 1 fair, and 1 poor result)	3
Postoperative reflux of bowel gas demonstrable radiographically in upper urinary tract (air pyelograms)	0

PRESENT CLINICAL RESULTS AFTER URETEROSIGMOIDOSTOMY

In table 11 is tabulated results obtained on the basis of pyelographic findings. Twenty-three patients were found to have an essentially normal upper urinary tract. Seven patients had a good result as evidenced by very slight but appreciable hydronephrosis or hydro-ureter on one or both sides. Three patients were found to have moderate to severe hydronephrosis on one or both sides, but with good renal function. It is likely that re-implantation, ureterostomy, nephrostomy or implantation into an ileal loop will ultimately be necessary to keep these patients well. Three patients have been frank failures and two have required external diversion of one or both kidneys. The third patient with pyelonephritis mentioned above died before drainage was necessary.

An analysis of the results in terms of individual kidneys is given in tables 12 and 13. It will be noted that 43 of 67 ureters (36 patients) were found on postmortem examination or by excretory urography to be excellent (normal), 12 were good (slight hydronephrosis), 5 were fair, and 7 were poor. If we consider the 12 good results acceptable we find 82 per cent acceptable results.

TABLE 13. *Final results in 67 separate ureterosigmoid transplants*

Excellent	43
Good	12
Fair	5
Poor	7

TABLE 14. *Correlation of pyelographic findings after ureterosigmoidostomy with postoperative blood biochemical studies (20 cases)*

Result	No Biochemical Disturbance	Hyperchloremic Acidosis
Excellent (normal upper urinary tract)	11	0
Good (slight but appreciable persistent hydronephrosis)	2	1
Fair (moderate to severe persistent hydronephrosis but good dye excretion in pyelograms)	0	1
Poor (failures)	1	1

A further consideration of the pyelographic findings is interesting. There were 10 pelves and ureters which showed significant dilatation prior to operation which returned to normal after uretero-enterostomy. Twenty-four renal pelves and ureters which were normal before operation showed no evidence of dilatation afterwards. There were 9 ureters and renal pelves which showed slight temporary postoperative dilatation which subsequently returned to normal. There were 11 normal renal pelves and ureters which showed slight but permanent dilatation subsequent to uretero-enterostomy, classified as good. Four renal pelves and ureters which were normal prior to operation have shown permanent moderate to severe dilatation but with good renal function, classified as fair. Six preoperatively normal ureters are failures. Three renal pelves and ureters which were dilated preoperatively have shown some persistent dilatation which has been classified as a good result in one, fair in one, and poor in one.

We have never noted any postoperative urographic evidence of gas in a ureter or renal pelvis, and barium enemas obtained occasionally have never demonstrated reflux of barium into the ureters. The longest period of observation is nearly five years. Patients have continued to do well. It would appear that in general when a good result has been obtained, little if any change occurs as the years have gone by.

HYPERCHLOREMIC ACIDOSIS

The discussion during the last few years relative to the frequency and cause of hyperchloremic acidosis after uretero-intestinal anastomosis has made it desirable to study this series of cases to determine the incidence of significant electolyte disturbance Our first observation is relative to blood urea nitrogen levels after operation. These were obtained every 2 days on the average after operation. Of 37 patients who lived reasonable periods after operation or who recovered, 28 showed no elevation of blood urea nitrogen, 8 showed slight elevation, and only one marked elevation (a patient with lower nephron nephrosis).

The correlation of blood electrolyte determinations of sufficient frequency to be of value in determining whether the patient had or did not have hyperchloremic acidosis, and pyelographic findings, was possible in 20 patients. The results of this correlation are given in table 14 and show that in 11 patients in which the upper urinary tracts were normal after operation there were neither clinical nor chemical signs of hyperchloremia. In 2 patients with good but not perfectly normal upper urinary tracts there was no evidence of hyperchloremia. In 4 other patients, also considered good, clinical and laboratory evidence of mild hyperchloremic acidosis was present. These patients had to force fluids and occasionally to take sodium bicarbonate. In one case hyperchloremic acidosis developed after unusual exertion on a hot day but promptly recovered when fluids were given. One patient with a fair result has mild acidosis controlled by fluids, alkali and frequent rectal evacuation. Two patients with poor anatomical results were studied. One has never had any signs of the syndrome (it must be admitted that renal function is still good), while the other required careful watching because of rather severe acidosis but has been subsequently relieved by bilateral nephrostomy.

These observations make possible the observation that if renal function is normal prior to ureterosigmoidostomy and if a nearly normal functioning ureter results from operation there is little likelihood of troublesome acidosis. On the other hand, if there is impaired renal function (low renal reserve) to start with or if tubular function is impaired as a result of operation either because of obstructive changes or infection or both, the incidence of troublesome hyperchloremic acidosis will be quite high.

It is fair to state that in our opinion uretero-enterostomy utilizing the intact bowel should not be done unless renal function is essentially normal or can be expected to return to normal if a good result is obtained. In the same vein it must be just as clearly understood that if the anatomical functional result after uretero-enterostomy is not acceptable some other type of urinary diversion must be considered and ultimately performed if poor health and ultimate death from renal failure are to be averted. It may be that the transplantation of ureters into an ileal loop may be very helpful in treating uretero-enterostomy failure. Occasionally an early poor result may be converted into an acceptable one by temporary nephrostomy and should probably be done more often. Decompensation of a ureter and renal pelvis of severe degree will not right itself without drainage.

CONCLUSIONS

The mortality, complications, and late results obtained from uretero-enterostomy performed by the Coffey 1 technique on 25 patients are briefly summarized.

The technique of the 'combined' uretero-enterostomy is restated and illustrated.

The results obtained to date of its use in 40 patients have been analyzed for mortality, early and late complication, secondary operations, anatomical results, incidence of hyperchloremic acidosis.

30 Bennet St., Boston 11, Mass.

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A NEW OPERATION FOR CREATION OF AN ARTIFICIAL BLADDER WITH VOLUNTARY CONTROL OF URINE AND FECES

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The need for diverting the urinary stream poses a dilemma for the urologist to which at present there is no fully satisfactory answer. He may sacrifice longevity for the sake of preserving the patient's volitional control over feces and urine, or he may sacrifice volitional control for longevity.

The operation presented here aims at satisfying both of these requirements.

THE AUTHORS' OPERATION

Basic features. The operation consists of using the isolated rectum as a new bladder, and creating a new rectum by mobilizing the sigmoid colon to sufficient length to permit its being pulled through the perineum immediately anterior to the anus but under the external sphincter ani muscle. This muscle thus encircles both the anus (outlet for urine) and the sigmoid stoma (outlet for feces), providing complete separation of the streams, together with voluntary control of feces and urine. There are other advantages: The patient is not conscious of an artificial orifice in an unnatural site; the new bladder may easily be cystoscoped, and a total cystectomy may be performed, if indicated.

Preoperative preparation. Proper bowel sterilization before surgery is of extreme importance, due to the fact that open anastomosis of the ureters to the gut is performed, with emphasis on obtaining a secure suture line. This can only be safely accomplished when bowel sterility is assured. The fear of contamination is entirely justified when the fecal and urinary streams are again to be joined; but when the rectal ampulla is a sterile container, never to be contaminated by feces, one is warranted in departing from conventional modes of anastomosis in which the ureter is plunged hastily into a small hole in the bowel, or anastomosis is tediously performed with poor exposure and no assurance that patency has been established. We therefore elected to treat the new bladder as such, and perform ureteral anastomosis with the rectum open (as in a routine ureterocystostomy). The extreme importance of proper bowel sterilization under these circumstances is obvious.

In preparing the bowel, we have followed the excellent system of intestinal antisepsis outlined by Poth, who advises that the surgeon be familiar with some of the serious complications which might arise from the use of intestinal antibiotics, especially the "choleriformic syndrome" arising from intestinal enterotoxins. In his extensive studies, Poth found the most effective antiseptic to be neomycin. In a small percentage of cases (10 per cent) there appeared an overgrowth of A. aerogenes. This can be suppressed by phthalylsulfathiazole (thalamyd) taken with the neomycin. In addition, Poth found it impossible to grow

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bacteria from a bowel flooded with 1 per cent neomycin solution 30 minutes before operation.

We therefore combine the regimen of intestinal antisepsis advocated by Poth with flooding of the lower bowel with neomycin solution:

1) The patient is placed on a nonresidue diet.

2) At 1:00 p.m. of the day before operation, 60 cc of castor oil, 1.0 gm. of neomycin and 1.5 gm. of phthalylsulfathiazole are given.

3) At 2:00 p.m., 3:00 p.m. and 4:00 p.m., 1.0 gm. of neomycin and 1.5 gm. of phthalylsulfathiazole are given.

4) Every 4 hours after this until operation, 1.0 gm. of neomycin and 1.5 gm. of phthalylsulfathiazole are given.

5) One hour before surgery, the lower bowel is flooded with 1 per cent neomycin solution through a catheter. This is held in the rectum and sigmoid to the time of operation.

Technique of operation. The patient is placed on the table in the supine position.

A transverse incision is made in the lower part of the abdomen. The peritoneum is opened, and all layers of the incision are opened from angle to angle.

The patient is then placed in the Trendelenburg position. The small intestines are packed off, exposing the rectum, sigmoid, pelvic parietal peritoneum, and urinary bladder.

Incisions are made in the pelvic parietal peritoneum on each side of the rectosigmoid. Both ureters are identified, dissected free, and transected as far distal as possible. No crushing clamp is placed on the proximal end of the ureter. Both ureters are intubated with 7F polyethylene catheters and the urine allowed to drain away from the operative site. Different colored catheters are used, to identify urine from the right or left kidney.

The site of transection of the rectosigmoid is determined by ascertaining the lowest level at which the ureters may be easily transplanted. At the selected site the mesocolon is opened to admit two Payr intestinal clamps, and the rectosigmoid is transected.

A traction suture is applied to each angle of the proximal sigmoid, to hold the bowel up as the Payr clamp is removed. All neomycin solution is removed by suction, to prevent spillage into the peritoneal cavity. The proximal end of the sigmoid is then closed with a temporary continuous suture. All sutures are gathered in a clamp and laid aside.

A traction suture is applied to each angle of the distal bowel (rectum), which is held up by assistants as the Payr clamp is removed. All neomycin solution is suctioned away.

The rectal ampulla (new bladder) is now ready for ureteral anastomosis. A mucosa-to-mucosa technique has been used by us, with good results. However, we do not advocate any particular method of anastomosis over others.

A sharp-nosed clamp is introduced into the open rectum and pushed through the wall at the desired site. The intubating ureteral catheter is grasped by the clamp and pulled into the rectal lumen, drawing the ureter to the bowel wall. Using No. 00 atraumatic chromic catgut, a mucosa-to-mucosa anastomosis is

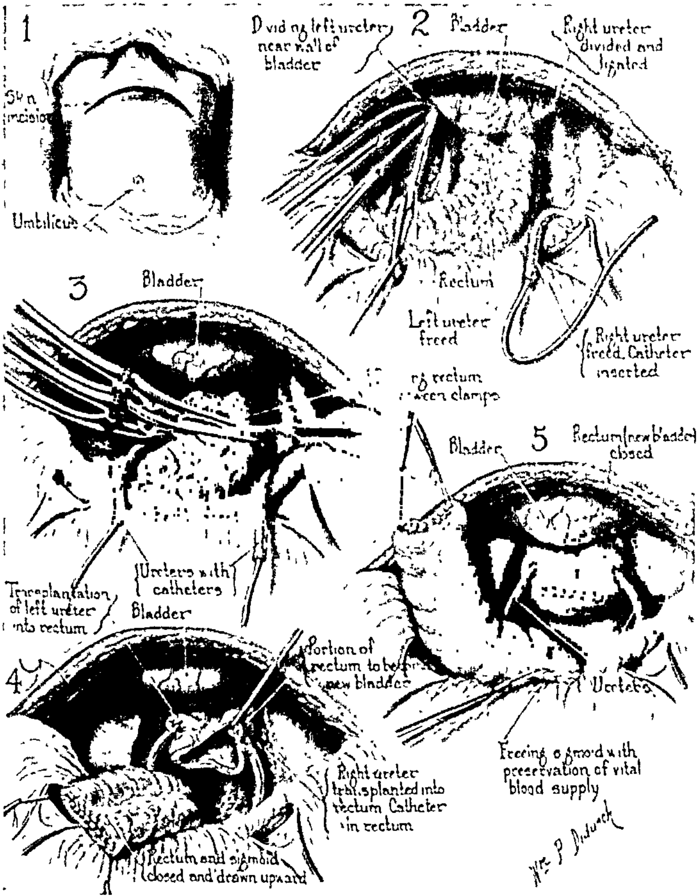
1
Skin incision
Umbilicus
Dividing left ureter near wall of bladder
2
Bladder
Right ureter divided and ligated
Rectum
Left ureter freed
Right ureter freed. Catheter inserted
3
Bladder
ng rectum
ween clamps
Transplantation of left ureter into rectum
Ureters with catheters
Bladder
5
Bladder
Rectum (new bladder) closed
4
Portion of rectum to be new bladder
Ureters
Right ureter transplanted into rectum Catheter in rectum
Freeing of sigmoid with preservation of vital blood supply
Rectum and sigmoid closed and drawn upward

FIG. 1. Lowsley-Johnson operation for diversion of urine, with voluntary control of urine and feces; first, or abdominal, stage of procedure. *1*, Skin incision. *2*, Ureters exposed. Right ureter transected near bladder and intubated with polyethylene catheter. Left ureter being divided. *3*, Rectosigmoid transected between Payr clamps. *4*, Proximal sigmoid closed with temporary suture. Right ureter has been transplanted over splinting catheter; left ureter being transplanted. *5*, Both ureters transplanted; distal rectosigmoid closed, completing new bladder. Freeing proximal sigmoid from mesocolon and vessels to permit it to be drawn through rectovesical space and perineum.

performed over the catheter. The end of the catheter is then tucked into the rectal ampulla splinting the anastomosis. (This is later drawn through the anus manually and fixed in position.) A similar procedure is performed on the opposite ureter.

The rectum is now closed with a layer of continuous atraumatic No. 00 chromic catgut sutures, followed by an interrupted serosal layer of the same material. This completes the new bladder.

The next step is to free the proximal sigmoid of attachments and provide enough length to allow it to pass through the rectovesical space, under the external sphincter ani, and out the perineal incision. This involves transection of branches of the sigmoid artery, with preservation of the secondary arcades to supply collateral circulation to the end of the bowel. If the arcades are interrupted, necrosis of the perineal stoma will result. Exactly how much length is required, and how many branches of the artery to transect, must be left to the surgeon's judgment. Considerable mobility can be obtained by dissecting free the peritoneal attachments of the fixed, or iliac, segment of the sigmoid. It may even be necessary to go as high as the splenic flexure, divide the phrenicocolic ligaments, and swing the entire descending colon medially. Mobility of the pelvic

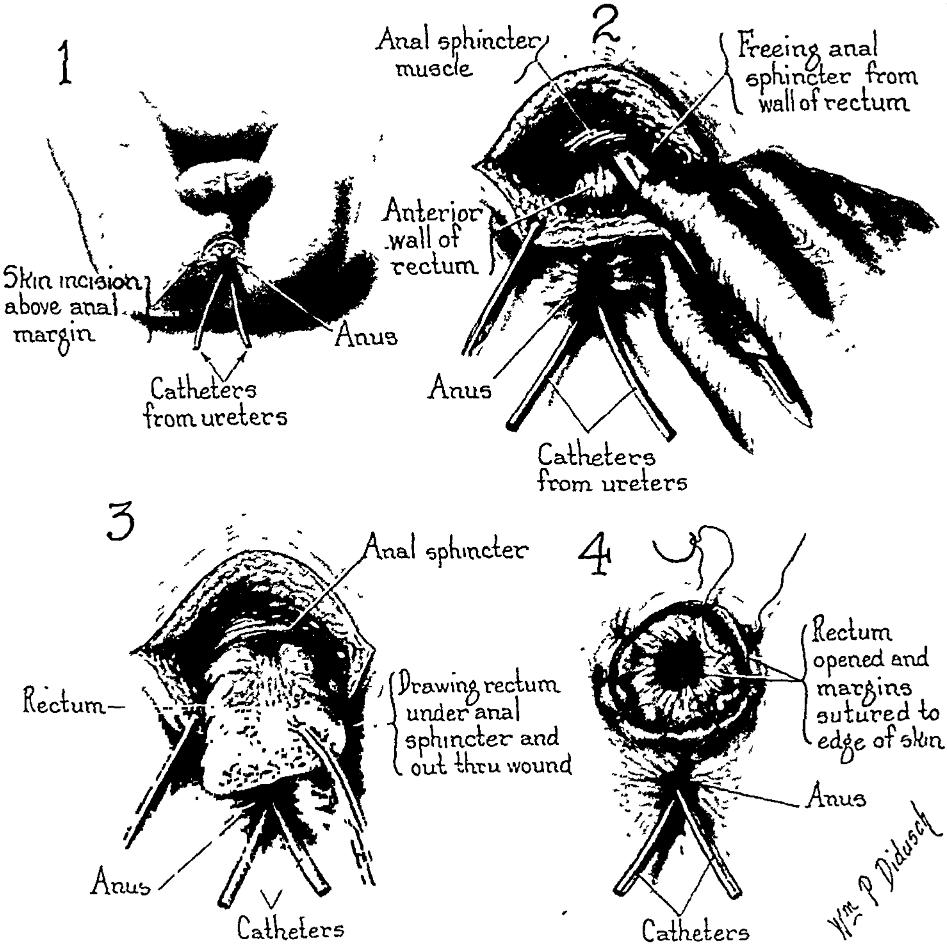
1
Skin incision above anal margin
Anus
Catheters from ureters
2
Anal sphincter muscle
Freeing anal sphincter from wall of rectum
Anterior wall of rectum
Anus
Catheters from ureters
3
Anal sphincter
Rectum
Drawing rectum under anal sphincter and out thru wound
Anus
Catheters
4
Rectum opened and margins sutured to edge of skin
Anus
Catheters
Wm P Didusch

FIG. 2. Second, or perineal, stage of operation. *1*, Patient in lithotomy position. Showing skin incision directly over anus. *2*, Dissection carried between rectum and external sphincter ani to rectovesical space. *3*, Proximal sigmoid drawn through rectovesical space and into perineal wound by traction sutures (not clamp, as illustrated). *4*, Temporary sutures closing proximal sigmoid opened, and mucosa of proximal sigmoid approximated to skin edge with interrupted sutures

segment of sigmoid is hampered almost entirely by vascular supply; mobility of the iliac segment, by lack of mesentery and by peritoneal attachments.

When adequate length of sigmoid has been attained, the patient is placed in *the lithotomy position, an assistant remaining above. A semicircular incision is* made 1½ to 2 cm. anterior to the anus, with the convexity anterior. An index finger in the rectum helps to guide the dissection, which is carried under the external sphincter ani muscle to the recto-urethralis muscle. Sharp dissection should be used in transecting the recto-urethralis, after which the rectum may quite easily be retracted posteriorly, exposing Denonvilliers' fascia in the male. Further dissection under the base of the bladder leaves only peritoneum separating *a finger in the rectovesical pouch above from the operator's finger below.* Long cervical packing forceps are passed through the peritoneum from below into the rectovesical pouch. After the peritoneal incision has been widened sufficiently, the assistant above places the traction sutures on the sigmoid and a long Penrose drain into the jaws of the forceps, and the sigmoid and drain are pulled through the incision and out the perineum.

The temporary suture closing the bowel is removed and the sigmoid sutured *to the borders of the perineal incision with interrupted sutures of No. 00 chromic* catgut. The sigmoidal mucosa has been pulled 1 to 2 cm. beyond the skin edge, to insure any necrosis of the extreme end of the bowel from extending into the incision and involving the vital external sphincter ani. While this protective measure has no effect on continence, it does leave some redundant mucosa which may be resected later. Further experience will probably allow direct mucosa-to-skin suturing, as there has been no evidence of terminal sigmoidal necrosis.

With *completion of the new rectum, a finger is inserted into the anus (outlet* of the new bladder) and the ends of the splinting ureteral catheters are withdrawn. An 18F rubber catheter is inserted into the anus and sutured in position to the skin. The splinting catheters are then fixed to the indwelling rubber catheter.

The patient is returned to the original supine position and the abdominal incision closed, preferably with drainage from above as well as below. Through-and-through wire closure *may be used, if desired.*

Postoperative follow-up. At the present writing, there are 2 patients with more than 6 months *of follow-up. The first operation of this type was performed on* July 3, 1953, and the second on August 7, 1953; therefore, these patients are in their ninth and eighth postoperative month, respectively. Both had transitional cell carcinoma of the bladder for which cystectomy was performed, the first patient having a one-stage and the second a two-stage procedure. Neither has shown recurrence of malignancy, allowing follow-up study of the function and performance of the new bladder and rectum.

Of prime importance is that both have voluntary control over feces and urine. Two or 3 movements of formed stool, and 4 to 8 urinary voidings daily, are the rule There is no involuntary loss of urine or feces while lying, sitting, walking, or working, and no dressings or special apparatus are required. Voiding and defecation often occur together but may occur separately, and one patient states that

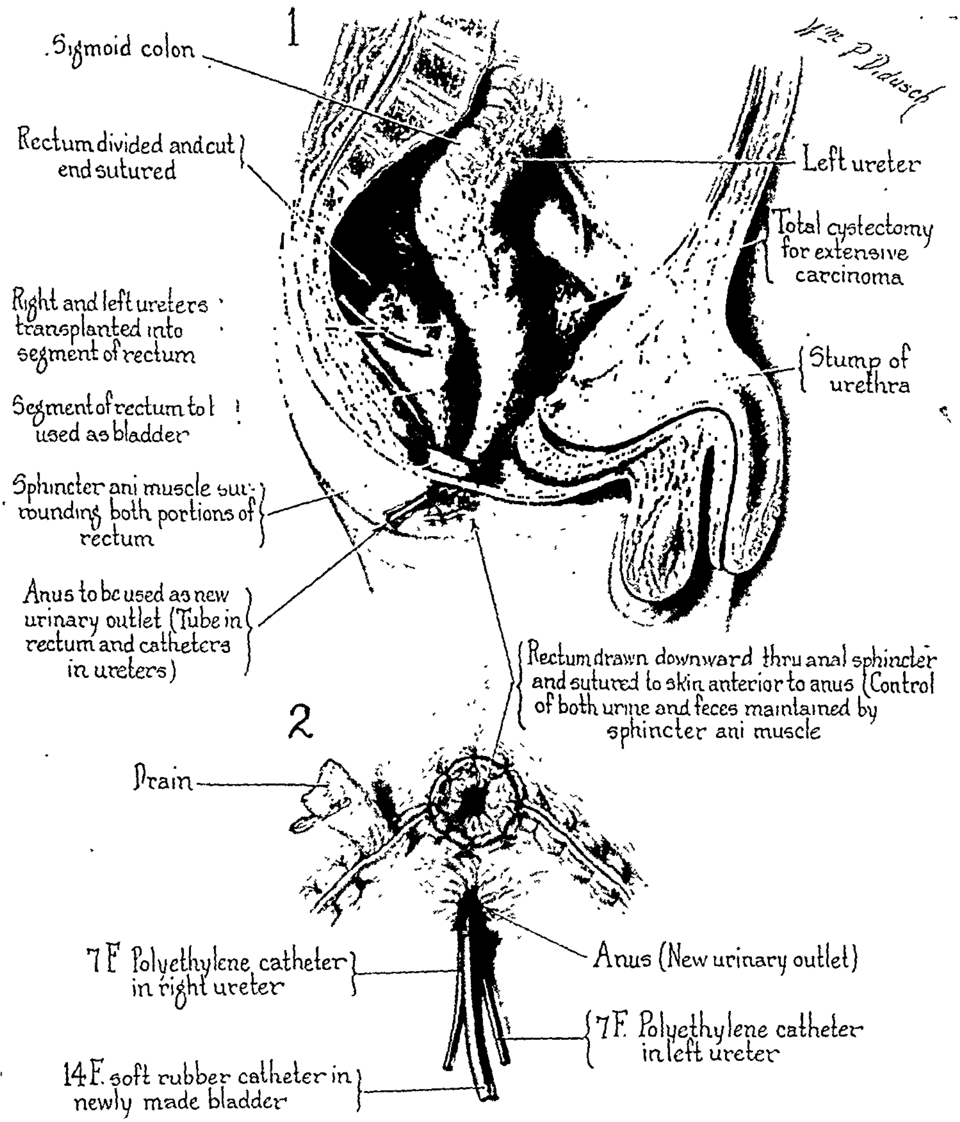
1
Sigmoid colon
Rectum divided and cut end sutured
Left ureter
Total cystectomy for extensive carcinoma
Right and left ureters transplanted into segment of rectum
Stump of urethra
Segment of rectum to be used as bladder
Sphincter ani muscle surrounding both portions of rectum
Anus to be used as new urinary outlet (Tube in rectum and catheters in ureters)
Rectum drawn downward thru anal sphincter and sutured to skin anterior to anus (Control of both urine and feces maintained by sphincter ani muscle
2
Drain
7F Polyethylene catheter in right ureter
Anus (New urinary outlet)
7F Polyethylene catheter in left ureter
14F soft rubber catheter in newly made bladder

FIG. 3. Sagittal section showing end result of operation, and relation of new bladder (rectum) to new rectum (proximal sigmoid). Fecal orifice is immediately anterior to urinary orifice (original anus), and both are under control of external sphincter ani. *2*, Appearance of perineum at completion of operation. Courtesy of the *Journal of the International College of Surgeons*.

he is conscious of the difference and can hold his urine while defecating, or vice versa. This phenomenon at present defies explanation.

Observation of these patients in the nude, front and rear, fails to reveal the new orifice, which is thrown into view when the patient bends from the hips. The new rectum in both has redundant mucosa, due to the precaution of leaving 1½ to 2 cm. of sigmoid beyond the edge of the incision. While this has in no way inconvenienced either patient, a direct approximation of sigmoidal mucosa to the skin edge would eliminate it. Secondary repair has been suggested for cosmetic purposes.

An examining finger in the new rectum palpates a tone very similar to that of the anus, and the patient can, on command, constrict the palpating finger with the external sphincter ani muscle. Neither patient has any evidence of stricture. A barium enema demonstrates good control of the sphincter over the opaque medium.

Catheterization (under sterile conditions) of the anal opening to the new bladder has shown insignificant residual urine after voiding. The bladder capacity in both cases is 300 to 350 cc, and the desire to void occurs at over 200 cc. The urine is clear, with shreds of mucosal material. Repeated examination of centrifuged specimens of urine have shown from 0 to 10 white blood cells per high power field. Cultures have been sterile as a rule. The second patient complained once of frequent voiding, the urine was found to contain 40 to 60 white blood cells per high power field, and a culture yielded B. proteus. This condition responded to antibiotics.

Cystoscopic examination has been accomplished easily in both bladders and the ureteral orifices located by indigo carmine intravenously injected. Attempts at ureteral catheterization have thus far been considered unwise.

Cystograms show good sphincteric control over the bladder contents. One patient has mild hydro-ureter and hydronephrosis—due, probably, to an increase in pressure in the rectum as compared to the normally low pressure in the urinary bladder. If such is the case, it is to be expected; and the prognosis in reflux of sterile urine must not be confused with that when urine is contaminated. Why our first patient has no hydro-ureter in the face of normally higher pressure in the rectum is not clear, unless a valvular action, preventing reflux, has been created unwittingly at the site of anastomosis.

The blood chemistries of both patients have remained essentially unchanged since operation.

SUMMARY AND CONCLUSIONS

A new operation for urinary diversion, with separation of the urinary and fecal streams and with voluntary control of urine and feces, is described.

The importance of proper preoperative preparation is stressed, and the necessary steps are given in detail.

The first two patients operated upon by this procedure have been followed up for 9 and 8 months respectively at the present writing. The follow-up shows that these two cases are entirely satisfactory as regards control of both urine and feces, and elimination of the lesion which made urinary diversion necessary.

This procedure is indicated in any condition requiring urinary diversion, where the underlying pathological process is not likely to prove fatal in a short time.

It is our belief that this new operation offers a greater hope of longevity combined with patient comfort than any method of diverting the urine now in use.

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THE SEXUAL FUNCTION IN PARAPLEGIA

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An earlier paper reported on the sexual function in paraplegia, largely in terms of its neuromuscular manifestations, and reviewed briefly the neurophysiology involved.[1] The present discussion will amplify this by observations on 208 patients in addition to the 200 originally studied, and consider other aspects of sexuality in these people. Certain of the statements in the prior study will be subjected to modification, in the light of more complete knowledge, and an effort will be made to correlate some of the reports in the recent literature.

Generally speaking, the sexual function comprehends three major activities—psychic, gonadal, and neuromuscular. In a broad sense, the first of these is not fundamentally altered among paraplegic males, except in so far as may result from discomfort or debility. It is important to differentiate between what may be called purely intellectual sexual preoccupation, on the one hand, and that awareness, on the other, which is the result of somatesthetic stimuli from the genital or other erogenous areas.[2] Some individuals, even when carefully questioned, may be unable to make this distinction and, in consequence, admit to a loss of interest when what they really mean is a loss of libidinous excitation. It has been suggested that such manifestations as walls adorned with pin-up girls, interest in erotic literature, and occasional attempts to caress nurses or female attendants, all of which seem to be about as prevalent among paraplegics as among other men of their age, are merely examples of whistling in the dark—attempts on the part of the patient to assure himself of his own continuing maleness. But it can just as well be argued that the continuance of these efforts over months and years, even without the reward of libidinous sensation, is sufficient evidence that psychosexual activity exists. This is a type of inquiry in which too detailed probing, in the case of a given individual, may result in false impressions through his inability to define psychosexual experience in comparison with remembered experience of somatesthetic origin. For that reason—although it may depend upon intangible factors which defy graphic representation—a long and intimate experience with a large group of these people, during which they are seen every day, all their problems intimately discussed, and a careful study of their personal feelings and reactions made part of their regular treatment, is more valuable than sharply delineated interviews with a few, however skilled the interviewer and however competent his interpretations. Based upon such an experience with something over 700 paraplegic males, the impression persists that once this difficult distinction between somatesthetic excitation and purely psychic activity has been made, the sexuality of these men on the psychic level is essentially unaltered. Again, allowance must be made for discomfort and debility

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Read at annual meeting [illegible] New York, N. Y. June 2, 1954.

[1] Talbot, H. S.: A repo[illegible] Urol., 61: 265, 1949.

[2] Herman, M.: Role of [illegible] sexual excitation in men. Arch. Neur. and Psych., 64: 42, 1950.

Nor can it be denied that pathological tendencies may become manifest if a patient is unable to make a suitable adjustment to his disability, but such changes in the group here reported are rare.

Gonadal disturbances associated with spinal cord injury have been the subject of a number of reports during recent years. Many seem to be offered on a *post hoc propter hoc* basis when, in fact, the causal relationships are by no means clear. Cord injury represents a serious trauma associated with a variety of secondary consequences, early and late, any of which may lead to changes in body economy. To determine whether a significant alteration may be of primary or secondary etiology is not merely academic; such an analysis is of great clinical importance. For many of the sequelae of cord injury are preventable, and it is desirable to be able to reduce to a minimum those effects which are inevitable and inescapable.

Discussions of the gonadal changes are usually based upon observed changes in the testicle or the occurrence of gynecomastia. The incidence of testicular atrophy in paraplegia has been widely reported, and attempts have been made to attribute these changes to a direct neurogenic factor.[3] There is, however, insufficient evidence, either anatomical or physiological, to support such conclusions firmly, although they are not necessarily wrong. Kuntz[4] has been unable to demonstrate nerve filaments penetrating the tunica propria of the testicle. He found changes in the testicles of dogs after removing the inferior mesenteric ganglia and the sympathetic nerves accompanying the spermatic artery, but believed these to be due to disturbances of vascular function. Mitchell found the innervation of the testicle and epididymis so complex that it was impossible to delineate its exact derivations.[5] Kuntz further concluded, after carefully analyzing his previous experimental work, that the possible causal factors in testicular atrophy, other than those associated with the direct experiment, were extremely complex and that any condition materially affecting the general physiologic state might be a factor in testicular degeneration. This has also been a common clinical observation, which materially increases the difficulty of demonstrating a direct neurogenic causation for the atrophic changes in the testicles. In many of the cases reported, such general factors are noted, and when they are not specifically mentioned, their existence may be assumed to the degree usually encountered among these patients. They include malnutrition, anemia, chronic infectious processes, and secondary parenchymatous changes such as atrophic pyelonephritis and amyloid disease. These and other conditions leading to or associated with marked debility are commonly followed by testicular atrophy. Another factor is the relationship of changes in the gonads to pituitary disease. McCullogh and others found such changes and considered that the degree of tubular damage was relative to the degree of deficiency of pituitary gonadotrophin stimulation as reflected by the urinary excretion of F S H.[6] Incidentally, they made other observations of considerable clinical interest One was that the testicular size appeared to be determined by the size and number of the seminiferous tubules, as revealed in the biopsy. The other was that the size of the prostate correlated fairly well with the number of Leydig cells Finally, their testicular biopsy material revealed no histological characteristics by which primary testicular failure could be differentiated from that secondary to pituitary disease In view of the alterations in pituitary function associated with severe trauma and shock, a mechanism is suggested for those changes in testicular structure which have been reported as occurring very soon after spinal cord injury. Klein and his co-workers, for instance, found marked modifications in the lining of the germinal epithelium as early as the fourth and the tenth days[7] They report on only a few cases, and they were unable consistently to reproduce similar alterations experimentally in rats

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[3] Stemnerman, G. N., Weiss, L., Auerbach, O. and Friedman, M.: A study of the germinal epithelium in male paraplegics. Am. J. Clin. Path., **20:** 24, 1950.

[4] Kuntz, A.: Degenerative changes in the seminal epithelium of the mammalian testis. Endocrinology, **5:** 190, 1921.

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Kuntz, A. and Morris, R. E., Jr.: Components and distribution of spermatic nerves and nerves of vas deferens. J. Comp. Neurol., **85:** 33, 1946.

[5] Mitchell, G. A. G.: The innervation of the kidney, ureter, testicle, and epididymis. J. Anat., **70:** 10, 1935.

Histologically, as reported by various authors, the testicular findings vary all the way from minor degrees of maturation arrest to definite structural atrophy which has every appearance of being irreversible The last factor, however, is difficult to prognosticate In other studies on testicular dysfunction and atrophy, a rather remarkable degree of reversibility, both functional and anatomical, has been observed[8] It is of further interest to note that in most of the reports dealing with paraplegics, the atrophy involves particularly the germinal epithelium, the interstitial structure remaining relatively normal This would appear to eliminate a vascular cause, in a recently completed study, no such predilection was found with demonstrated vascular involvement, the germinal and interstitial elements being similarly affected[9] The longest, most carefully studied, and best documented series of cases showing testicular changes in paraplegics is that published by Bors and his co workers[10] Abnormalities were observed in the germinal epithelium of 31 of 34 patients, the most constant findings being those associated with various degrees of spermatogenic arrest In 7, the histological alterations suggested permanent structural damage, 22 were classified as showing "secondary atrophy" and the findings were described as "not dissimilar to those in the testes of hibernating animals with seasonal cryptorchid testes" Such an observation, of course, suggests functional reversibility Seeking a neurological basis, the authors suggested the possibility of the influence of alterations in the heat regulatory mechanisms and thought they could establish a correlation between the testicular findings and changes in the sweating mechanism. It was suggested that this might explain the continuation of normal menstruation in female paraplegics, the ovaries being notably less sensitive to temperature changes than the testes.

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[6] McCullogh, L P, Gold, A and McKendry, J B R Alterations in testicular structure and function in organic disease of the pituitary J Clin Endocrinol 10: 871, 1950

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Barton, M and Wiesner, B P Significance of testicular exfoliation in male infertility Brit Med J 2 938, 1952

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[10] Bors E, Engle, E T, Rosenquist R C and Holliger, V H Fertility in paraplegic males J Clin Endocrinol, 10. 381, 1950

Bors, E Perception of gonadal pain in paraplegic patients Arch Neur and Psych, 63: 713 1950

It was considered possible, however, that a hormonal as well as a purely neurogenic factor might be responsible for alterations in the gonads. The urinary excretion of 17 ketosteroids was normal to high in these cases (an observation made in another study as well),[11] and the possibility was considered that this might represent adrenal hyperactivity in response to the various alarming stimuli to which these patients are subject, in the form of complications. The urinary estrogen levels were also high, while the urinary gonadotrophin levels were consistently low. The biopsies had shown essentially normal testicular interstitial elements, and liver function tests revealed nothing to suggest diminished destruction of circulating estrogens. Such adrenal cortical hyperfunction might impair spermatogenesis either by alteration of the pituitary-gonadal axis or by the direct action of androgens on the germinal epithelium, the secretion of gonadotrophins meanwhile being inhibited by the relatively high levels of estrogens and androgens. No mention is made in this study of gynecomastia or other significant alterations in the secondary sexual characteristics, and it is a safe inference that no such changes were noted.

On the basis of available evidence, the testicular changes cannot be specifically attributed to a neurogenic factor, but are such as might arise from the general or hormonal disturbances associated with injury or disease of the spinal cord. Further, by analogy with similar changes occurring in other non-paraplegic patients, there is reason to believe that these alterations may be reversible. It seemed logical at this point to try to elucidate the problem by investigating paraplegic females in terms of their menstrual function. Recent literature contains few references to this, probably because traumatic paraplegia is so much more common in males. Cooper mentions briefly that female paraplegics cease to menstruate for three to six months after injury and have scanty menstruation thereafter, but offers no further details.[12] Four young paraplegic women personally observed all continued to menstruate normally after injury, and this has been so in a number of others who have been the subjects of personal communications from their physicians. The menses, of course, may be altered or suppressed in women who are anemic or debilitated, so that, here again, the possibility of a systemic rather than a neurological background for the dysfunction must be considered. Pursuing this inquiry further, a study was made of nine female paraplegics, ranging in age from 12 to 22 years.[13] Eight had had cord lesions since birth, not entirely analogous, perhaps, to traumatic lesions, but all associated with the musculoskeletal and visceral disorders commonly seen with spinal cord injury. Seven of these eight patients had normal menstrual histories. The eighth, at age of 14, has not yet menstruated. The one traumatic case in this group is a 22-year-old woman who sustained her cord injury at the age of 19. Catamenia was normal before injury and has continued normal since. By the evidence in females, therefore, it would appear that there is no obvious and direct connection between injury to the spinal cord and gonadal function. There have, of course, been a number of reports of paraplegic women conceiving and bearing children. Malnutrition may also be a cause of secondary amenorrhea. Many women with previously normal menses stopped menstruating during periods of relative starvation in occupied countries. Improvement in food restored normal menstruation in all of them without any further hormonal therapy.

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[11] Cook, A. W. and Lyons, H. A.: Urinary excretion of 17-ketosteroids in paraplegics. U. S. Armed Forces Med. J., **1:** 583, 1950.

Staub, P. L., Menthe, J. *N*., Nelson, S. S. and Cohn, H.: Excretion of 11 oxycorticosteroids in paraplegic and rheumatoid arthritic patients. J. Clin. Invest., **29:** 349, 1950.

[12] Cooper, I. S. and Hoen, T. I.: Metabolic disorders in paraplegics. Neurology, **2:** 332, 1952.

[13] Dr. Hathorn P. Brown has very kindly provided this material from a study carried on at the Massachusetts Hospital School, Canton, Mass.

Gynecomastia has been reported in paraplegic males, but the frequency of its occurrence seems to vary widely in different series of cases. Cooper mentions an incidence of 22 per cent, three unilateral cases and four bilateral, in a series of 32 patients.[14] In only one of these was malnutrition prominent, but detailed information is not given as to the general condition of these patients in other respects, particularly with regard to chronic infection. Reference is made to the complex described by Klinefelter, Reifenstein and Albright,[15] but no evidence offered to suggest that these cases fall into the same category. Grabstald and Swan[16] found a closer analogy to that syndrome in cases of testicular atrophy in leprosy. This is apparently a specific type of orchitis with widespread fibrotic and obliterative changes, involving the interstitial as well as the germinal elements. Gynecomastia in association with malnutrition is well known and was observed frequently in liberated prisoners of war at the end of World War II. It has been suggested that in these instances, there are specific alterations of the pituitary-gonadal axis associated with the lack of proper amino acids and certain vitamins, notably the B complex and E. It was interesting that in many instances, the gynecomastia appeared when normal nutrition was resumed, which is explained as follows by Polymenakos: "When these factors are again supplied, the activity of the endocrine system, and especially the hypophysis, increases, with augmented secretion of gonadotrophin and prolactin, causing the same effect as in adolescence. There is firstly stimulation of the breast tissue with gynecomastia and, secondly, stimulation of the testis with increased production of androgens. This increase of androgens inhibits hormonal secretion by the hypophysis and restores normal function of the hypophysis testis axis. This probably causes the disappearance of the gynecomastia."[17] Other metabolic disorders occur in paraplegics, usually as a result of prolonged inactivity and other complicating factors, and these may be associated with gynecomastia, although the relationship is obscure.[18]

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[14] Cooper, I. S. and Hoen, T. I.: Gynecomastia in paraplegic males. J. Clin. Endocrinol., 9: 457, 1949.

Cooper, I. S., MacCarty, C. S. and Rynearson, E. H.: Gynecomastia in paraplegic males. J. Neurosurg., 7: 364, 1950.

[15] Klinefelter, H. F., Jr., Reifenstein, E. C., Jr. and Albright, F.: Syndrome characterized by gynecomastia, aspermatogenesis, etc. J. Clin. Endocrinol., 2: 615, 1942.

[16] Grabstald, H. and Swan, L. L.: Genito-urinary lesions in leprosy. J. A. M. A., 149: 1287, 1952.

[17] Polymenakos, L. G.: Post-starvation gynecomastia. Lancet, 1: 1021, 1952.

Among the patients who provided the material for this study, gynecomastia was seen in only a few instances, three of them actual castrates. With an average census of 135–150 paraplegics and quadriplegics, it has not been seen on the wards for something over two years. There were not more than half a dozen cases in the 408 patients whose neuromuscular function is covered later in this study. Apparently, therefore, gynecomastia is also nonspecific as far as the cord injury is concerned, and arises in relation to secondary sequelae. Furthermore, none of these patients has shown any evidence of change in other secondary sexual characteristics, and this applies also to the female patients already mentioned. A few cases of eunuchism have been reported, but very few considering the large number of paraplegic patients now under observation. In this series, it occurred only in those who had been castrated.

Thus, of the factors that comprise the sexual function, the psychic and the endocrine element of the gonadal may remain fundamentally unaltered by spinal cord injury, if the patient can be kept in good physical condition and can make a satisfactory adjustment to his new way of life. Spermatogenesis is frequently impaired, and the neuromuscular function is drastically modified. No significant new material, either factual or theoretical, seems to have been published since the prior report on this subject already mentioned, concerning the neurophysiology of the sexual function in males. Excellent discussions of this interesting and rather involved mechanism, however, have been provided by Whitelaw and Smithwick, and by Rose,[19] in connection with observed alterations after various types of sympathectomy.

Sexual activity in man subserves two functions: first, the obvious biological requirement of reproduction; and, second, a complex need for personal expression and gratification with all the psychological, social, and aesthetic implications thereto attached. The latter is apparently the more compelling in our society, and certainly among the patients whose cases are here reviewed, there was more interest in potency than in paternity. This is not to suggest that none of these men is interested in fathering children. It is, with a considerable number of them, an important preoccupation, as is attested by the number who have gone through the complicated processes of adoption when they find themselves sterile. This may arise from one or more of three factors. First, the failure of spermatogenesis, whatever its cause; second, the obstruction of the genital passages in consequence of infection spreading from the lower urinary tract; third, the neuromuscular dysfunction, particularly failure of ejaculation. In spite of this, every clinic treating any considerable number of paraplegics has reported the occurrence of pregnancies among their wives, although the fact that these instances are so reported is in itself sufficient evidence that they are unusual There have been, by present reckoning, nine such pregnancies, at least, reported from the group of about 100 patients discharged from Cushing V A Hospital A very conservative allowance for unreported cases, for the large number of patients still unmarried, for those in the older age group, and for those who have died, would permit at least the doubling of this figure, and thus establish a fertility rate of 5 per cent or better Special attention to individual cases might improve this even more Unfortunately, the desire and the capacity for paternity do not always coincide, making not only for individual disappointments, but for difficulty in evaluating the level of fertility in the group as a whole [20]

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[18] Cooper, I. S., MacCarty, C. S., Rynearson, E. H. and Bennet, W. A.: Metabolic consequences of spinal cordectomy. Proc. Staff Meet. Mayo Clin., **24:** 620, 1949.
Cooper, I. S., Rynearson, E. H., MacCarty, C. S. and Power, M. H.: Metabolic consequences of spinal cord injury. J. Clin. Endocrinol., **10:** 858, 1950.

[19] Whitelaw, G. P. and Smithwick, R. A.: Some secondary effects of sympathectomy. N. Eng. J. Med., **245:** 121, 1951.
Rose, S. S.: An investigation into sterility after lumbar ganglionectomy. Brit. Med. J., **1:** 247, 1953.

But since, as has been said, this desire appears in only a small number, it is perhaps more important to consider sexuality in its broadest manifestations, and as it meets the requirements of most of the members of the group This calls for an investigation of the neuromuscular phase of sexual activity in some detail Such a study has been carried out in a series of 408 paraplegic and quadriplegic patients with levels of neural involvement varying between the fifth cervical segment and the cauda equina All were males, most of them young, and in the majority, the cord lesion was of traumatic origin

The series is divided into two groups of 200 and 208 patients, respectively, each having been treated at a Veterans Administration Paraplegia Center, the first at McGuire V A Hospital in Richmond, Virginia, and the second at Cushing V A Hospital in Framingham, Massachusetts The only essential difference is that since the Cushing group was studied a few years later, it included a larger proportion of patients with paralysis of longer standing This is probably of little significance since the pattern of sexual function in these patients is established fairly early, and tends to remain the same, unless altered by neurosurgery or long debility In both groups, about 75 per cent were still in the hospital when studied, the remainder having been discharged to their homes Many of those still hospitalized had been out of the hospital on leaves and thus had an opportunity, whether or not they had seized it, to put their abilities to the test

The data were gathered by individual questionnaires, answered under a pledge of anonymity The questions were simply worded so as to be easily understood and answered Yes or No For those who wrote their replies in the hospital, a doctor was available to interpret the questions if necessary The same assistance was available by correspondence to those who replied by mail There was little difficulty in this respect and the attitude of the patients was universally one of interest and co operation The 408 tabulated were drawn from a total of 413, only 5 having been rejected because of obscurity In both groups, all the questionnaires had been collected before tabulation was begun, and none was in any way altered or "interpreted" Questions left unanswered were considered as answered in the

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[20] Munro D , Horne, H H and Paull, D P The effect of injury to the spinal cord and cauda equina on the sexual potency of men N Eng J Med , 239 903 1948
Horne, H H Paull, D P and Munro, D Fertility studies in the human male with traumatic injuries of the spinal cord and cauda equina N Eng J Med , 239 959, 1948

TABLE 1. *Etiology*

	McGuire	Cushing
Trauma	190	196
Tumor	4	
Pott's disease	1	
Syphilis	1	
Diabetic arteriosclerosis	1	
Myelitis—undetermined	3	
Multiple sclerosis		4
Spinal anesthesia		1
Polio		1
Epidural abscess		2
Hodgkin's disease		1
Hematomyelia		2
Guillain-Barre		1
Total	200	208

negative. As already noted, the actual tabulations were done three years apart, and not compared until the second had been completed. The results in the two groups show a remarkable degree of correlation, and it is, therefore, probable that the total of 408 represents a reasonably adequate sample of this class of patients.

Table 1 shows the etiology of the cord lesion in both series of cases. Table 2 illustrates the incidence of survival of the erectile function, broken down into two groups: those whose erections can be produced only on a reflex basis by local stimulation, and those who respond to psychic stimulation as well. The latter may be presumed to have incomplete lesions, although in a large number of them, a complete transection is present to all intents and purposes. In table 3 an attempt is made to relate the survival of the erectile function to the level of the cord lesion. The cases were sub-divided at various levels until one was found at which there seemed to be a significant difference between those with lesions above and lesions below. Since the reflex centers for neuromuscular sex function are located in the lumbosacral portion of the cord, it is not remarkable to observe that the closer the lesion is to these segments, and the greater consequent risk of their involvement, the more likelihood there is for interference with this function. Table 4 summarizes other aspects of neuromuscular sex function. It shows, as might be

TABLE 2

	McGuire		*Cushing*	
	Number	Per cent	Number	Per cent
No erection	73	36½	65	31
Local stimulation	85	42½	101	49
Psychic stimulation	42	21	42	20
Total	200		208	

TABLE 3

	Not Given		D11 and Above		D12 and Below	
	McG	Cush.	McG	Cush	McG	Cush
No erection.	11	3	26	32	36	30
Local stimulation	4	3	59 } 75%	76 } 75%	22 } 53%	22 } 60%
Psychic stimulation	3	—	20	19	19	23

TABLE 4

	Local		Psychic	
	McGuire	Cushing	McGuire	Cushing
Total.	85	101	42	42
Sensation	22	9	37	25
Ejaculation.	6	12	17	20
Noct. Emission	11	10	12	13
Intercourse	19	21	27	27
Ejaculation	4	4	16	13
Gratification.	6	6	22	19

expected, that there is a closer approach to normal in the group which retains the capacity to evoke erections by psychic stimulation than in those who retain only the reflex response. The first listing for ejaculation covers those cases in which this could be accomplished by manipulation. The second represents those in which it occurred during intercourse. The figures for intercourse include only those who had satisfactory intromission and a reasonable duration of erection. They are probably too low, since a very considerable number of the patients had not even made the attempt at the time the questionnaires were answered. It will be noted again, as might be expected, that in the "psychic" group, the number retaining libidinous sensation is relatively high, as is the case also with those reporting gratification during intercourse. This, however, was not necessarily of a normal voluptuous character. In the "local" group, it was usually described as a vague sense of satisfaction, not associated with normal libidinous pleasure, and sometimes even in spite of some discomfort. In the treatment of impotence generally, it has been noted that a large number of patients are less disturbed by the loss of voluptuous gratification than by a sense of inadequacy. So it is that among

TABLE 5 *Interval between injury and first erection, 132 patients, Cushing group, traumatic*

Less than 1 mo	19	76 per cent
1 to 3 mos	49	
4 to 6 mos	33	
7 to 9 mos	6	
10 to 12 mos	19	
13 to 18 mos	1	
19 to 24 mos	2	
Over 2 yrs (longest 3½)	3	

paraplegics the ability to have sexual intercourse, even in the absence of normal sensation, seems to be a source of considerable satisfaction.

Table 5 is confined to traumatic cases since a specific starting point for the cord lesion could be accurately established in these, and is drawn from the Cushing group only. It demonstrates what has been suggested by many observers in the past—that in better than three-quarters of these patients, the pattern of neuromuscular sex function is established within six months. In only 5 per cent of those who had erections at all was the first delayed for over a year.

SUMMARY AND CONCLUSIONS

About two-thirds of a series of over 400 paraplegic and quadriplegic patients studied were found capable of having erections, in most cases reflex in character, but in about one out of three subject also to being evoked by psychic stimulation. Return of this function has usually occurred within six months after injury.

Of the patients who had erections, about one-third had had intercourse and more than half of these reported a sense of gratification. Since the majority of these people were still hospitalized while the investigations were being carried out, these figures are probably conservative.

It would appear that about 5 per cent of these men are fertile.

The psychic aspect of sexuality usually remains unimpaired. The endocrine factor of gonadal function is likewise unchanged and there are, therefore, no modifications of secondary sexual characteristics. Alterations in the germinal epithelium and varying degrees of spermatogenic arrest are common. Although this may be the direct result of the neurogenic factor, it is more likely to be a consequence of a deteriorated general condition or hormonal imbalance.

Considering the sexual manifestations as a whole, it is apparent that the popular belief that all of these men are totally inadequate is unjustified. In view of the survival of a number of the components which go to make up the total function, it is possible, by careful study and treatment of the individual patient, to develop a reasonably satisfactory type of sexual activity. This has already been done in a number of instances and should be done in a great many more. Its importance to the patient's rehabilitation and well-being requires no emphasis.

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CYTO-DYNAMIC PROPERTIES OF URINARY NEOPLASMS: V, CULTIVATION *IN VITRO* OF TRANSITIONAL CELL EPITHELIUM

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It was felt that the behavior of normal transitional cell epithelium *in vitro* should be studied since a great number of urinary neoplasms arise from this parent epithelium and their biological behavior is poorly understood. Indeed, the so-called "seeding" of papillary transitional cell carcinoma may well be a semantic trap. Perhaps a carcinogen is secreted in the urine, and certain areas of transitional cell epithelium are more susceptible to its action or are rendered more susceptible by co-carcinogenic activity. This view has been expressed by many. It is proposed to study the behavior of normal transitional epithelium *in vitro*, and this report is concerned with such epithelium from the upper two-thirds of the prostatic urethra.

METHOD

Large pieces of hypertrophied, intravesical prostatic gland were obtained with the resectoscope, and the urethral transitional cell epithelium (fig. 1, *A*) stripped away under aseptic conditions. The strips were then cut up into small fragments, approximately 1 mm. square, in balanced salt solution to which 0.0025 mg. of streptomycin had been added. Two additional washings were made with the fragments remaining in each solution for 20 minutes.

Each fragment was then mounted on a flying coverslip in rooster plasma to which 2 drops of medium (4.5 parts of balanced salt solution, 4.5 parts of placental cord serum, and 1.0 part of 50 per cent chick-embryo extract) were added. The coverslip was then inverted over a well slide and sealed with paraffin. Incubation was at 37°C.

OBSERVATIONS

For 48 hours there were numerous epithelial cells about the explant, and then extensive proliferation of sheets of epithelium began. By the seventh day, it was extensive (fig. 1, *B*). At this time the cultures were fixed by methyl alcohol and stained with May-Grunwald mixture followed by Giemsa solution. Detailed cytology is shown in figure 1, *C*.

The outgrowth was sheet-like and of one cell thickness. The nuclei were ovoid, located centrally in the cystoplasmic mass, contained single, often concentric nucleoli, possessed prominent chromatin network and thick, and at times, beaded nuclear membranes. The cytoplasm was abundant, and the nuclear-cytoplasmic ratio was equal to that of cells observed in smears similarly fixed

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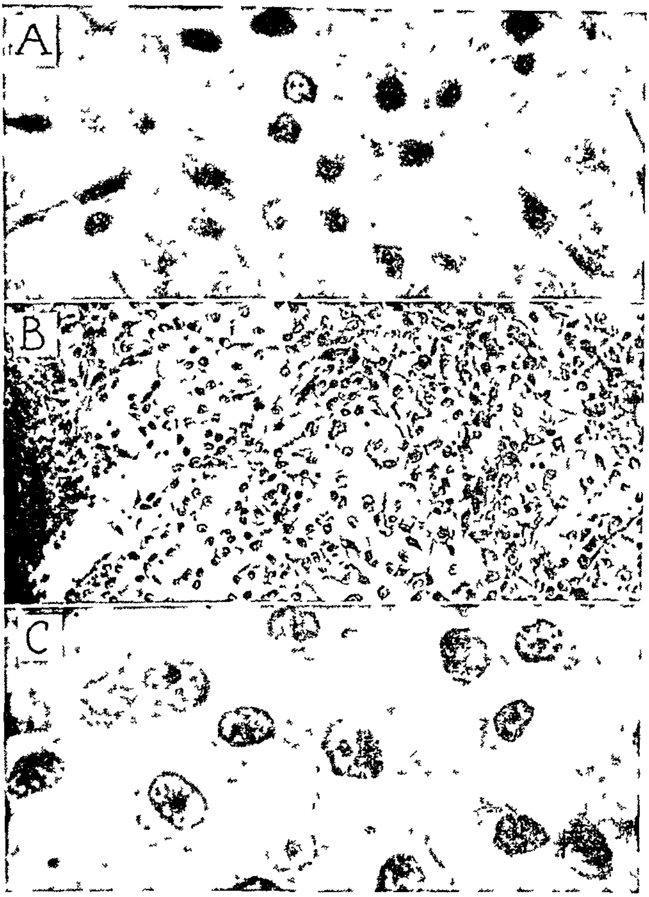

FIG. 1. *A*, oil immersion view of original explant of transitional cell epithelium *B*, low power view of stained culture showing sheet of new proliferating cells *C*, oil immersion view of stained cells in outgrowth

and stained from normal transitional cell epithelium Only an occasional double-nucleated cell was noted.

SUMMARY

Transitional cell epithelium obtained from the upper two-thirds of the prostatic urethra grew well in tissue culture and cytological details are noted.

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LEIOMYOSARCOMA OF BLADDER: THREE CASE REPORTS AND A REVIEW OF LITERATURE

JOHN D. SILBAR AND SIDNEY J. SILBAR

The history of sarcoma of the bladder dates back to 1861 when Senftleben[1] was the first to report a case. However, it was not until 1875 that a case of leiomyosarcoma of the bladder was mentioned in the literature by Gussenbauer.[2] Since that time sarcomas of the bladder have been found to be very rare. Pack and La Fevre[3] reported that they constituted only 0.38 per cent of all bladder tumors. Caulk[4] found only one sarcoma in 303 bladder tumors. Ratliff and Valk[5] reported three sarcomas in 562 bladder tumors seen at the University of Michigan Hospital. Thus, while vesical sarcomas are rare, the incidence of leiomyosarcoma of the urinary bladder is even more so. Review of the world's literature from 1861 until the present revealed only 27 cases.[7-29] Recently we had the opportunity to study three cases of leiomyosarcoma of the urinary bladder. The following are reports of our cases and a review of the previous literature on the subject.

CASE REPORTS

Case 1. A 20 year old white woman was admitted to the hospital on the surgical service 2 weeks postpartum. For the past 8 days the patient had been bleeding in profuse amounts despite oxytoxics and androgen administration. Complaints were also referable to the urinary tract in that the patient had fre-

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Accepted for publication March 17, 1954

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quency, urgency, and was passing gross blood in the urine. There had been a marked weakness to the degree that the patient had been unable to raise her head. Following the admission urinalysis, the diagnosis of acute hemorrhagic cystitis was made. Temperature upon admission was 103F and reacted favorably to antibiotic treatment. Blood was given, since the patient on admission exhibited 6 grams of hemoglobin and 2,500,000 red blood cells. A total of nine transfusions was given during the hospital stay. On the third hospital day cystoscopy was performed. The urine was grossly bloody and the bladder was full of clots. The capacity was normal. It was noted that the floor of the bladder was covered with a bullous edema and a mass was found on the left wall of the bladder, but this could not be differentiated because of the marked bleeding. Cystograms done at this time (fig. 1, *A*) showed the presence of a defect. Intravenous urograms were essentially normal. It is believed that the bladder defect was a large clot although an intrinsic lesion could not be ruled out. On the sixth hospital day the patient was taken to surgery where a cystotomy was performed through a Pfannensteil incision. A large bladder tumor was fulgurated and the bladder mucosa coagulated. The postoperative course was uneventful. Pathological examination revealed 25 grams of brittle gray tissue from the bladder (fig. 2, *A*). This low powered view of the first case shows sections of a very hemorrhagic sarcoma composed of irregular bundles of spindle-shaped cells, which are pleomorphic and have dark hyperchromic nuclei (fig. 2, *B*). This reveals a high powered view of the above in which we see spindle-shaped cells with marked variation in size and chromatin content of the nuclei. From these specimens the diagnosis of a leiomyosarcoma of the urinary bladder was made.

The patient was discharged from the hospital and re-admitted 5 days later. She was afebrile and taken to surgery on the third hospital day at which time a cystoscopy was again performed and a mass seen in the lower left region of the bladder. This measured 1½ by 1 cm. and was slightly raised above the bladder mucosa. This was thoroughly removed by means of transurethral resection.

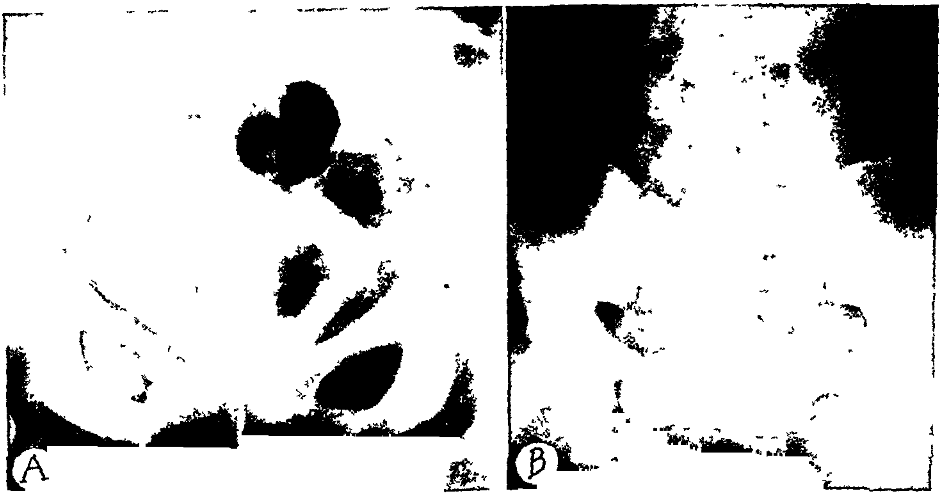

FIG. 1. Case 1. A, cystogram shows filling defect on left side B, follow-up cystogram

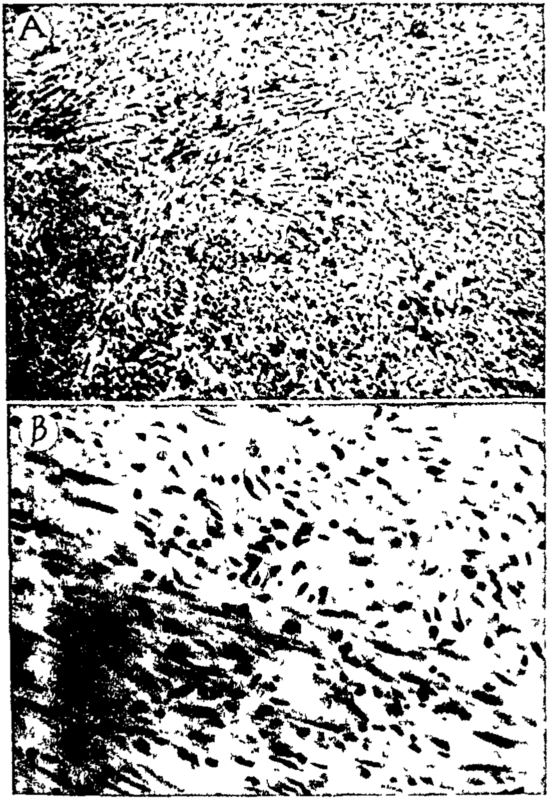

FIG. 2. Case 1. A, low power view showing hemorrhagic sarcoma composed of irregular bundles of spindle-shaped cells. B, high power view.

Microscopic pathological diagnosis again proved to be leiomyosarcoma of the bladder. The patient was asymptomatic following surgery and was discharged on the tenth hospital day.

Follow-up revealed that 3 years later the patient was entirely asymptomatic and there was no evidence of recurrence of the tumor either on cystoscopic examination, cystogram, or by vaginal examination. Figure 1, *B* shows the evidence of a normal cystogram.

Case 2. A 79 year old white woman on hospital admission stated that she was in apparently good health until approximately one month prior to admission when she noticed an increase in frequency, nocturia of 3–4 times. Associated with these symptoms she observed marked dysuria, suprapubic pain, and episodes of bloody and foul smelling urine. These symptoms were markedly increased in the 24 hour period prior to hospital admission. Past history was essentially negative. Physical examination revealed an elderly, poorly nourished, lethargic, rather pale, white female, whose blood pressure was 120/64. Other than the changes of aging, important physical findings were limited to abdominal and pelvic examinations. Pressure over the suprapubic area produced pain and the urge to void. Pelvic and bimanual examinations demonstrated a rounded, smooth, pendulous mass in the bladder area. During her stay in the hospital she ran a consistent low grade fever with an evening rise. Urinalysis showed a persistent pyuria with occasional showers of red blood cells. Urine cultures were reported as negative. The nonprotein nitrogen was 26 mg. per cent. Cystoscopy revealed a large, round mass with a gray-green surface which filled the bladder. Adequate visualization of the bladder wall could not be done because of the mass. It appeared that the mass was attached to the right lateral wall in the region of the ureteral orifice (fig. 3). Excretory urography showed dilatation and tortuosity of the ureters. The kidney pelves were dilated. A filling defect of the bladder with only a rim of dye outlining the mass was present. A few days after this the bladder was opened suprapubically. The previously noted tumor was delivered, the base resected, and fulgurated as completely as possible. Postoperatively the recovery was slow, but satisfactory except for bronchopneumonia which responded to antibiotic therapy. The suprapubic wound healed well and the patient was voiding easily with marked decrease in the entrance symptoms. One month later repeat cystoscopy showed some evidence of recurrence in the region of the right ureteral orifice and transurethral resection and biopsy were done. Figure 4, *A* is a low powered section of the specimen which shows it to

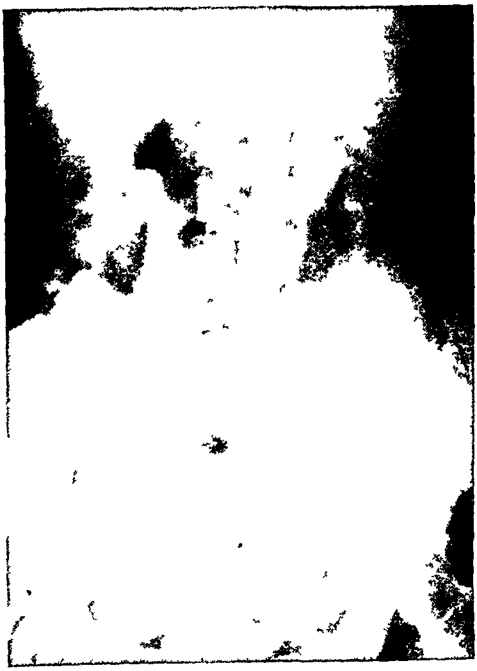

FIG 3 Case 2 Excretory urogram

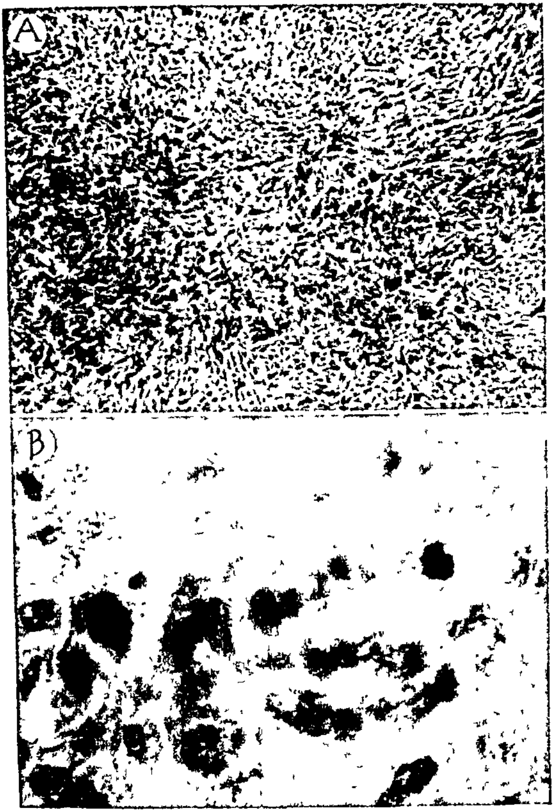

FIG. 4. Case 2. A, low power view. B, high power view

be composed of spindle-shaped cells, which are arranged in irregular groups because of the presence of numerous thin walled vessels. Notice that the nuclei vary in size and shape! They are hyperchromic and mitotic figures are present. Figure 4, *B* is a high powered section of the specimen which revealed marked nuclear variation and many mitotic figures to be present.

Case 3. A 68 year old white man was admitted to the hospital with a history of painless, gross hematuria of 3 week's duration. The episodes of bleeding were noticeable from slightly pink urine to passage of occasional small clots. The urological history was negative except for a large bladder calculus, which was removed surgically approximately two years prior to hospital admission. The patient states that the stone was about the size of a large walnut, smooth in surface, and black in color. Physical examination was entirely normal. Laboratory examinations were within normal limits. Cystoscopic examination showed a large fungating mass which extended over the posterior surface and base of the bladder. A diverticulum opening was seen in the center of the mass. Surgery was performed which consisted of a cystotomy. Electroresection through the mass liberated a large amount of thick green pus from multiple small ab-

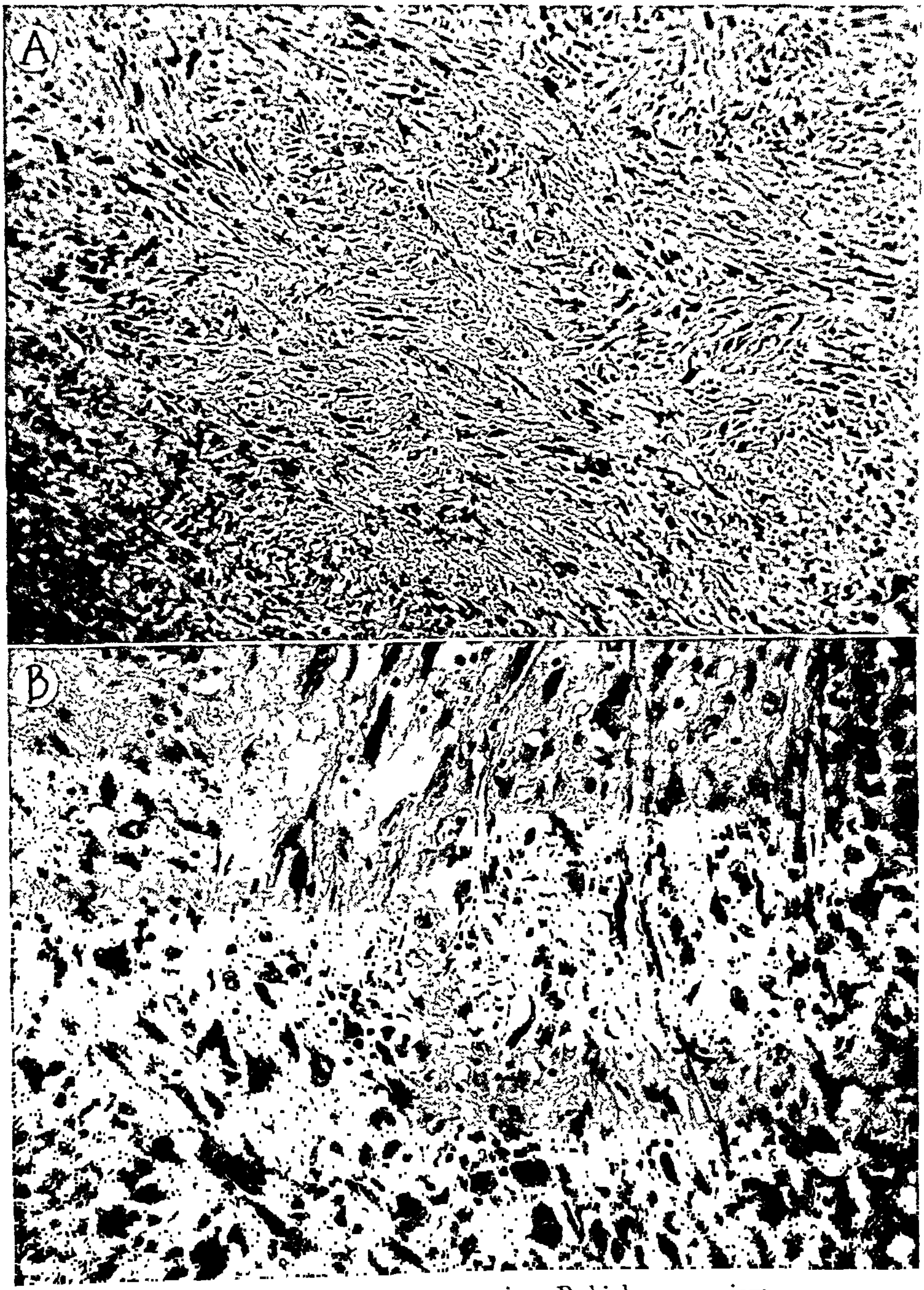

Fig. 5. Case 3. A, low power view. B, high power view

scesses. About 75 grams of tissue were removed and the base was coagulated. Pathological examination of the specimen revealed grossly the *specimen to have* a gray-white appearance and cut with a gritty sensation. Microscopic examination of the sections showed extensive destruction of the wall of the urinary bladder due to a very cellular tumor. Its pattern varied (fig. 5). Predominantly it represented interlacing bundles of spindle-shaped fibers, disclosing elongated *blunt shaped nuclei with a cross hatched pattern of the chromatin and a strongly* eosinophilic cytoplasm. There was considerable nuclear pleomorphism, but infrequent mitosis. In other areas the tendency to fasciculation disappeared and the cells assumed an epitheloid-like character. Large areas of hemorrhagic infarction were present. It was felt that we were dealing with a highly malignant sarcoma with *its origin in the smooth muscle of the urinary bladder*. Postoperatively the patient made an uneventful recovery, was dismissed from the hospital on the eighth postoperative day. One week later the patient suffered a cerebrovascular accident and expired. Unfortunately, a postmortem examination was not obtained.

DISCUSSION

The origin or stimulating factor of the leiomyosarcoma has not been established. However, there are many theories as to its origin. It may be from a partially atrophied mullerian body,[30] from the urachus,[31] from the supernumerary ureters,[32] from the hydatid of Morgagni, or the lower layer of the utricle, or it may develop from hypertrophied vesical musculatures, secondary to chronic inflammatory changes.[33] However, until any of these theories can be definitely proven, the etiology of vesical sarcoma is best explained in the works of Cohen.[34] Smooth muscle tumors may arise in the adult by unrestrained growth of misplaced persistent mesenchymal cells.

PATHOLOGY

Morphologically the sarcoma may have many types: lympho, fibro, chondro, lipo, osteogenic, rhabdo, and leiomyosarcoma. We will restrict ourselves only to the description of leiomyosarcomas. Grossly, they may be single or multiple, pedunculated or sessile. They are usually large, soft, and friable with ulcerative areas frequently present. The tumor grows very rapidly. They originate in the submucous or muscular layers of the bladder wall, then become intravesical and also invade the organs of the pelvis. The leiomyosarcoma is a vascular growth and therefore, appears reddish-gray, especially when viewed cystoscopically. Microscopically the tumor consists of long fusiform cells similar to those of smooth muscle. These are arranged in whorled bundles. The cells are slightly eosinophilic in character and have long oval hyperchromic nuclei The connective tissue may become edematous and infiltrated with round cells or disappear in the actively growing tumors while formation of giant cells of very large dimensions takes place. The tumor may undergo necrosis, hemorrhage, or myxomatous degeneration. As in the case of carcinoma, there have been various attempts to classify the leiomyosarcoma as to its malignancy. This was probably best done by Proper and Simpson, who called grade 1 those tumors that closely resemble a leiomyoma, these being the least malignant; grade 2, those tumors having short spindle-shaped cells with oval nuclei; most malignant were grade 3, those tumors that have a great deal of variation in cellular structure.

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[30] Verhoogen Quoted by Kretschmer and Doerhing.
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LOCATION

The location of the tumor is very important in differentiating a leiomyosarcoma from a rhabdosarcoma. A review of 18 cases of rhabdomyoma and rhabdomyosarcomas by Khoury and Speer[35] reported that nearly all the tumors were those from the trigone. However, in the case of a leiomyosarcoma none of the tumors were seen in the trigone except those that filled the entire cavity. The locations of the tumors were: dome or superior portion, 3 cases; left lateral wall, 5 cases; right lateral wall, 7 cases; posterior wall, 8 cases; filled bladder, 6 cases; location not given, 1 case.

These findings show that a leiomyosarcoma will have its origin in the wall of the bladder rather than from the trigone.

AGE AND SEX

Herman[36] said, "Vesical sarcomas are most frequent before the tenth year and after the fiftieth year." In our review of 30 cases this theory is not verified. The ages of our patients were: unknown, 2 cases; 0 to 10 years, 3 cases; 10 to 50 years, 12 cases; 50 to 70 years, 13 cases. The tumor does not have a predilection for any one sex. In this series there were 18 males and 12 females. This shows that nearly 50 per cent of the patients were in the 10–50 years of age group.

SIGNS AND SYMPTOMS

There are no diagnostic signs or symptoms. Twenty-one of the 30 cases had gross hematuria. Every case except one had a urological complaint which would indicate the need for a cystoscopic examination. Cystoscopy will reveal the presence of a bladder tumor. It is usually impossible to be able to differentiate between a sarcomatous lesion and a carcinoma except histologically. In our series the signs and symptoms were: hematuria, 21 cases; frequency, 10 cases; dysuria, 9 cases; suprapubic pain, 7 cases; palpable mass, 2 cases; inguinal pain, 1 case; difficulty in voiding, 1 case; no signs or symptoms (lesion found on autopsy), 1 case; symptom not mentioned, 1 case.

PROGNOSIS

The prognosis of sarcomas in general is very poor. The mortality rate is much higher than that of patients having carcinoma. In former articles, Smith and Kellert[24] believe that the mortality for sarcomas was nearly always 100 per cent,

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[35] Khoury, E. N. and Speer, F. D.: J. Urol., **51**: 505, 1944.

[36] Herman, Leon: Practice of Urology. Philadelphia: W. B. Saunders Co., 1938.

TABLE 1. *Duration of life after diagnosis and cause of death*

	Cases
Results not stated or follow-up not given	4
Death before one year	16
Unknown causes	4
From recurrence	3
Bilateral hydro-ureter and hydronephrosis	2
Ascending infection	2
Peritonitis following surgery	1
Anuria	1
Metastases to lung	1
Metastases to liver and inguinal region	1
Cerebrovascular accident	1
Living over one year	6
Living over three years	2
Living over four years	1
Living over ten years	1

and Lev and Bell[27] felt that the patient usually died within one year. We do not believe that the outlook is quite that bad any more (table 1). The tumor remains localized. Only 2 cases showed evidence of metastases. Therefore, the prognosis should be based on two important considerations: First, is the size of the tumor and location; second, is the degree of malignancy of the tumor cells.

TREATMENT

The only treatment of value for leiomyosarcoma is removal of the tumor and the surrounding bladder wall. Thus, if the tumor is small, extensive fulguration of the area or a partial resection of the bladder wall may be enough. However, if the tumor has invaded a great deal of the bladder, a total cystectomy, dissection of the inguinal nodes, and transplantation of the ureters would be indicated. Follow-up treatment with x-ray may be used. However, the tumor itself is radioresistant.

SUMMARY

Three cases of leiomyosarcoma have been presented.

A review of 27 previous cases has been presented and the results discussed.

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VESICAL ORIFICE OBSTRUCTION IN WOMEN AND ITS TREATMENT BY TRANSURETHRAL RESECTION

DAVID M. DAVIS

It is now generally recognized that obstructions at the vesical orifice and along the urethra are very common in females. Most of them are readily relieved by mechanical dilatation with large sounds or with the Kollmann dilator. A number of urologists have advocated treatment by transurethral resection when the narrowing at the vesical orifice does not yield to dilatation. Others advise against this operation, claiming that it is futile and dangerous, being too often followed by incontinence or vesicovaginal fistula.

It is my personal opinion that properly performed transurethral resection in women is a perfectly safe and satisfactory operation, and that it is indeed the only means by which cases resistant to dilatation can be cured. I shall endeavor to support this opinion by an analysis of 56 personal cases so treated.

Table 1 shows the grouping according to age, and the nature of the symptoms present. Of seven cases in children and adolescents—all certainly congenital obstructions—five had lower abdominal pain, and only three pain on voiding. Six had recurrent bouts of infection, and one a continuous, persistent (chronic) infection, while only four complained definitely of frequency, and in only two was there tangible evidence of difficulty or straining. Two dampened their clothes, probably a matter of marked urgency rather than real incontinence. In both cases the leakage stopped after operation.

In the 20 to 29 year decade only two of the 6 patients were married. In one of these the first attack of cystitis occurred at the time of marriage, but the attacks increased rapidly in severity and frequency, and culminated in complete retention. The other was a remarkable case, in that the obstruction at the vesical orifice was a part of a rare anomalous condition, namely, a bilocular bladder. The septum between the two bladder cavities was removed in addition to enlarging the vesical orifice, and an excellent result obtained. The three unmarried patients all had frequency and difficulty, two of them had recurrent infections, and the other had severe left kidney pain which persisted after transurethral resection had relieved the voiding difficulty.

The great majority of the cases come to treatment in the two decades from 40 to 59 years of age. Infection is a prominent feature in about half of these cases. In the others frequency, difficulty and pain make up the usual clinical picture, just as in contracture of the vesical orifice in the male. The nine cases in the three decades from 60 to 89 years of age are of quite similar type, three of them going to complete retention.

Table 2 shows what operations were performed. On examination all cases showed contracture of the vesical orifice of greater or less degree. In several there was what might well be called median bar formation. In three there were vesical diverticula, and several others showed varying degrees of visible muscular hy-

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Read at annual meeting, Mid-Atlantic Section, American Urological Association, Washington, D. C. April 22, 1954.

TABLE 1. *Ages and symptoms*

Symptoms	Age (Number of Cases)									
	0-9 (5)	10-19 (2)	20-29 (6)	30-39 (3)	40-49 (21)	50-59 (10)	60-69 (6)	70-79 (2)	80-89 (1)	Total (56)
Pain-Blad.	3	2	—	—	2	1	1	—	1	10
Pain-Void	2	1	3	1	10	4	6	1	—	28
Pain-1 Kid.	—	—	2	2	7	—	2	—	—	13
Pain-2 Kid	—	—	—	1	1	1	—	—	—	3
Pers't Inf.	1	—	—	—	1	1	1	—	1	4
Rec't. Inf.	4	2	4	2	10	5	2	—	—	29
Freq.	2	2	4	4	14	9	7	2	1	45
Diff.	1	1	4	3	10	4	2	1	1	27
C. R	—	—	2	1	2	1	1	2	—	9
Hemat	—	—	—	—	1	—	—	—	—	1
Kid. Stones	—	—	—	—	1	—	—	—	—	1
Leakage	2	—	—	—	1	—	—	—	—	3
Headache-hypertension			—	—	1	1	—	—	—	2

pertrophy and trabeculation. In thirteen cases there was marked stenosis of the external meatus, requiring meatotomy. In six cases the mid-portion of the urethra was strictured or narrowed enough to require internal urethrotomy. In 2 cases the obstructive lesion was complicated by urethral prolapse and in one by urethral diverticulum.

The operative enlargement of the vesical orifice was carried out with the McCarthy resector in 54 cases and both resector and punch were used in one case. A baby punch instrument was used on one little girl 4½ years old. Other procedures are shown in table 2.

In 6 patients the primary resection was thought to be inadequate. Four of them underwent two resections, two of them three resections. Two patients underwent nephrectomy before resection, one afterwards. This case is interesting. In a little girl resection did away with frequency and difficulty of voiding, and cleared a persistent, chronic bacillary urinary tract infection. However, left hydronephrosis was present due to ureteropelvic obstruction, and the chronic infection was re-

TABLE 2 *Operations*

	Primary	Secondary	Tertiary
Resection alone	34	4	1
Resection & urethral meatotomy	9	2	—
Resection & internal urethrotomy	1	—	1
Resection, meatotomy & urethrotomy	4	—	—
Resection & ureteral meatotomy, unilateral	3	—	—
Resection & ureteral meatotomy, bilateral	1	—	—
Resection & excision urethral diverticulum	1	—	—
Resection & excision urethral prolapse	2	—	—
Punch operation	1	—	—
Total	56	6	2

placed by infrequent recurrent infections. Left nephrectomy brought about complete permanent cure (11 years). In 2 patients intubated ureterotomy had been performed. In one patient a radical hysterectomy (Wertheim), performed shortly after resection, led unfortunately to bilateral ureterovaginal fistula. In one patient resection failed to halt a widespread leukoplakia of the bladder. This eventually gave rise to an epidermoid carcinoma for which cystectomy was performed.

As to results (table 3), I have ventured to describe them as follows:—

Perfect, 29 cases: No symptoms, no complaints, no nocturia, normal daytime intervals, bladder capacity normal, urine clear, sterile, and devoid of leukocytes or red cells.

Excellent, 5 cases: No complaints, no pain, urine sterile. These cases may fail to rate perfection by reason of an occasional night voiding, a few red cells in the urine, a failure to report recently for examination, or an insufficiently long postoperative period. Some of them may be potentially perfect results. One who had gone on to complete retention has now been through pregnancy and labor without the slightest difficulty.

Very good, 7 cases: Two of these patients report themselves as "well," but have not been examined. One shows very satisfactory relief, but is too recent for a better rating. Three are very well, but still require an occasional dilatation. One of these has been relieved of severe headaches, and her blood pressure has fallen from about 175 systolic to about 150 systolic. Another has been relieved of iritis. One has an almost completely paralyzed bladder, following extensive gynecologic operations, and requires a urethral dilatation about every two or three months, but is so greatly relieved that she is delighted. All have sterile urine.

Good, 6 cases: One of these cases has a contracted bladder due to the injection of some corrosive chemical after an abdominal operation years ago. She gets along famously with an occasional hydraulic distension under anesthesia. One is markedly improved, but has "occasional burning". Two write that they are "greatly improved", and two require occasional dilatations. Possibly these resections are not quite complete.

Fair, 4 cases: In one patient, 80 years of age, long-standing chronic infection of the urinary tract was permanently cured after resection, but bladder pain

TABLE 3. *Results*

	Cases			
Perfect	28	*	†	‡
Excellent	5			
Very good	7			
Good	6			
Fair	4			
Failure	2			
?	4			

* 33 cases, 58.92 per cent
† 40 cases, 71.42 per cent
‡ 46 cases, 82.13 per cent

persisted In a nun of 28 frequency and difficulty disappeared after resection, but left kidney pain remained A woman of 39 was perfectly well for over 2 years, but left kidney pain recurred at that time, and she did not return for further treatment One patient 77 years of age was perfectly well for 2 months, when difficulty recurred A second resection failed to improve matters, and the bladder was then found to be almost completely paralyzed She died in a few weeks of a chloride losing nephritis

Failure, 2 cases. One patient had very extensive leukoplakia Voiding was much improved and the frequency was less after resection, but the leukoplakia was not affected and eventually gave rise to epidermoid carcinoma In another case resection was performed in the hope of arresting recurring episodes of hematuria for which no other cause could be found, but the hematuria continued

Of the remaining 4 cases, three have been lost to observation, and all efforts to make contact with them have failed The fourth suffered bilateral ureterovaginal fistula and ureteral occlusion after a Wertheim hysterectomy One ureter has been re established and the bladder appears to function normally

Thus it is possible to report that at least 40 cases (71 42 per cent) have results "very good" or better, and 46 cases (82 13 per cent) have results "good" or better Of the 6 cases with unsatisfactory results, five received certain unquestionable benefits from the operation, but short of complete cure The 4 cases inadequately followed may provide some more good results

In the diagnosis of lower tract obstruction in the female one must question the patient very precisely, just as one does in the male, concerning the usual voiding symptoms, namely frequency, difficulty or straining, hesitancy, small, weak stream, interruption or multiple voiding, urgency, leakage of urine day or night, and pain or burning Females seldom volunteer information as to most of these symptoms, searching interrogation is necessary Complete retention is self evident Please note that it was present in 9 cases of 56 (16 43 per cent) Chronic hypogastric (bladder) pain is not at all infrequent Renal pain, bilateral or unilateral, is fairly frequent, and it is important to know that unilateral renal pain can be caused by vesical orifice obstruction, and does not necessarily imply unilateral ureteral obstruction or indeed any intrinsic lesion of the kidney or ureter Gastro intestinal symptoms may be prominent, although there happens to be no such case in this series One patient had acute iritis which disappeared after relief of the urinary obstruction and cure of the urinary tract infection In one patient hypertension was greatly reduced, and the headaches consequent upon it eliminated This pleasing result is unfortunately rare, and did not occur in the other case of severe hypertension, in spite of a perfect functional result One patient had passed small stones from a solitary kidney every few days for over eight years No further stones have formed since the vesical orifice was enlarged by resection 3½ years ago

No deaths and no operative accidents have occurred in this series There is no difficulty in avoiding trouble if one remembers that one is not concerned with removing large masses of tissue, as in operations on the prostate gland, but only with enlarging the orifice to its normal size One should therefore shave away tissue in thin layers, never cutting to the full depth of the loop This process is repeated until the desired point is reached. A finger in the vagina may be very helpful. If the removal is not quite adequate, it is always simple enough to take away a little more. In many cases the most gratifying results follow removal of amounts of tissue which seem ridiculously small to those accustomed to operate thus only on the prostate gland.

It should be stated that the convalescence after transurethral resection is often more uncomfortable in females than in males. The reasons for this are obscure. Some patients have practically no discomfort, but others may complain of burning and frequency for varying periods, occasionally as long as two or three months. This feature has no doubt discouraged a good many urologists from performing resections in females. The doctor's attitude must be confident, he must encourage the patient, he must help her as much as possible with bladder sedatives and he must calibrate the urethra from time to time to make sure there is no postoperative scar tissue contracture. He must hasten the eradication of infection by the proper and not excessive use of antibiotics. If he does these things he will obtain many extremely gratifying results.

All of the statements made concerning the symptoms and diagnosis of urethral and vesical orifice obstruction in females apply equally to a very large number of cases in which excellent results can be obtained by mechanical dilatation, alone or with the assistance of electrocoagulation of the urethral mucosa and of urethral meatotomy. When these simpler methods fail transurethral resection will practically always succeed. In this series all cases, with a few exceptions, had failed to respond to such methods before resection was resorted to. The exceptions were cases in which vesical diverticula or marked trabeculation were present. It was felt that such findings indicated severe degrees of obstruction, in which efforts at dilatation would be only a waste of time.

Transurethral resection is, of course, very valuable in the female as in the male when the expulsive force of the bladder is absent or subnormal due to neurogenic conditions.

In conclusion, it seems to me that this series of cases offers strong evidence that:

Transurethral resection is the only satisfactory and practical method to relieve lower urinary tract obstruction in the female which does not respond to mechanical dilatation.

Transurethral resection in the female is a safe procedure if the same precautions are observed as in the male.

Transurethral resection is helpful, by reducing urethral resistance, in neurogenic bladder in the female just as in the male.

Pain and/or infection in one kidney or in both may be relieved by enlarging the vesical orifice if there is no organic ureteral obstruction.

If there is an organic ureteral obstruction, the resulting stasis in the kidney may support a persistent infection from which recurrent attacks of cystitis may take origin, even if all lower tract obstruction has been eliminated. This fact should not prevent careful search for lower tract obstruction in all cases.

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SPONTANEOUS REGRESSION OF PULMONARY METASTASES ARISING FROM A TESTICULAR TUMOR

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The spontaneous regression of a primary malignant tumor or its metastases is a rare phenomenon. True spontaneous disappearance of neoplastic tissue should be differentiated from the therapeutic obliteration, as in the case of pulmonary metastases fading away following exposure to radiation therapy. The surgical excision of a primary tumor and roentgen therapy to metastatic nodules resulting in a cure is not a spontaneous manifestation. When distant metastases dissolve without any treatment other than laparotomy or operative removal of the primary tumor, then spontaneous regression may be acknowledged.

A benign tumor that presents spontaneous dissolution is the common skin verruca. Spontaneous cures of malignant tumors arising in organs other than the genito urinary system have been reported. Lange described the regression of a papillary adenocarcinoma of the ovary. Laparotomy and biopsy had revealed the nature of the tumor and the extensive abdominal metastases. The patient was returned home with a hopeless prognosis, but nearly three years later presented no evidence of the tumor or its metastases. Janker reviewed the literature in 1938 and briefly summarized 23 cases of spontaneous regression of malignant tumors and metastases. It was of interest to note that this occurred more frequently in cases with sarcoma than in carcinoma, at the ratio of 3:2.

Spontaneous regression of malignant tumors more often encountered by urologist are the bladder neoplasms that disappear following diversion of the urinary stream and the pulmonary metastases that on rare occasions disappear after nephrectomy for a renal cell carcinoma.

The choriocarcinoma has shown a greater tendency for spontaneous regression than any other specific neoplasm. Case histories reveal that metastases vanish more often than the original tumor focus. The metastases fade after excision of the primary growth. This has occurred predominantly in the female. Park and Lees, in 1950, were able to find 12 cases of spontaneous regression. Levi and Haig added 2 cases where pulmonary metastases disappeared after bombarding the primary uterine chorio epithelioma with deep roentgen therapy.

Craver and Stewart, Prym, Rottino and DeBellis have described the spontaneous healing of chorio-epithelioma in the testis. The patients expired as a result of extensive metastases, but on autopsy the original focal area in the testis was found to be replaced by scar tissue. Schofield presented a case report of a testicular tumor with multiple pulmonary metastases. The prognosis being poor, the patient was not subjected to orchiectomy or roentgen therapy. He was

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hospital complaining of marked weight loss, anorexia, weakness and dyspnea on exertion. Two weeks prior to admission he had noticed the presence of a slightly tender epigastric mass and several days ago, had noticed that both breasts were larger than usual. Physical examination revealed absent supraclavicular nodes. Both mammary glands were enlarged to plum size but nontender. Blood pressure was 110/70. The upper abdomen was distended by a hard, tender, smooth, fixed mass which extended to 1.5 cm. below the umbilicus and measured about 12.0 cm. in its horizontal diameter. The Friedman test was positive.

A chest roentgenogram revealed numerous round, well defined metastases throughout both lung fields. Their size varied from nut to plum size (fig. 1, *D*). Roentgenograms of the spine were negative, but films of the pelvis showed suspicious metastatic nodules in the left ischial ramus at the lateral aspect of the head of the left femur, and in the left acetabulum. The excretory urogram was normal. The patient was referred for roentgen therapy. Radiation was directed to the anterior and posterior chest, and to the anterior and posterior abdomen. Therapy was discontinued after 9 treatments because of marked leukopenia.

On April 24, jaundice developed and the liver was enlarged to 3 cm. below the costal margin. The patient deteriorated rapidly, and expired on May 24, 1950.

Necropsy revealed both breasts to be enlarged; metastatic involvement of both lungs, the right lung weighing 800 gm. and the left 725 gm. The liver was markedly enlarged, weighing 4,100 gm. and completely studded with innumerable metastatic nodules.

Microscopic examination of various nodules from the lungs, liver and retroperitoneal lymph nodes, all revealed essentially the same findings. The tumor

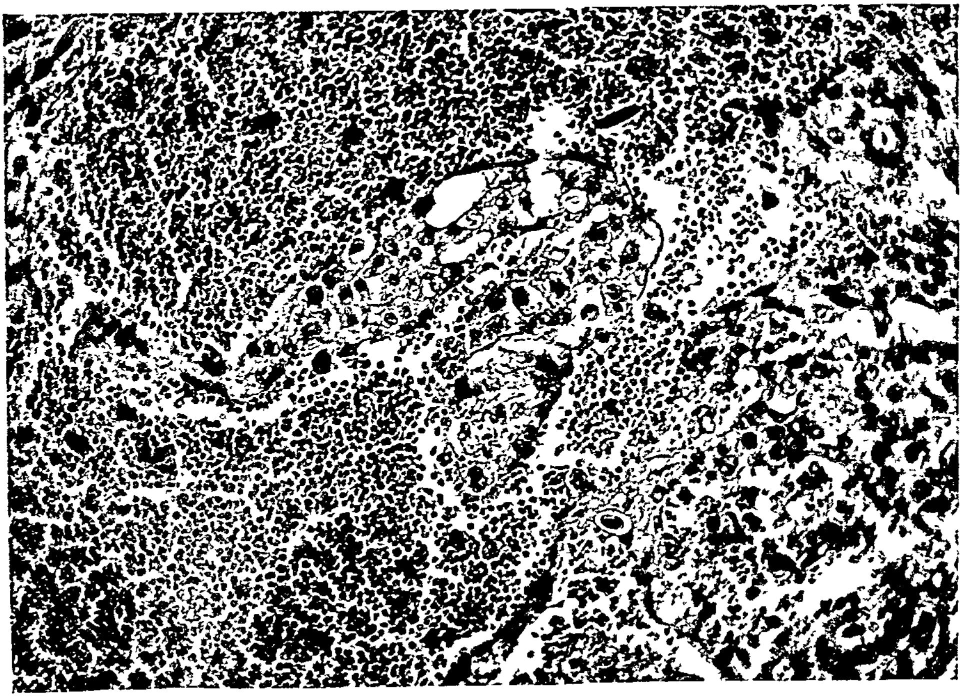

FIG. 2. Metastatic lesion in liver

showed hemorrhagic necrosis with scattered isolated groups of cells Most of these were syncitial cells which appeared large, pleomorphic, bizarre, multinucleated and contained a large amount of cytoplasm Clumps of Langhans or cytotrophoblastic cells of a polyhedral form were present and contained a clear cytoplasm with a relatively large hyperchromatic nucleus The surrounding tissue showed varying degrees of hemorrhagic extravasation and phagocytic infiltration (fig 2) The diagnosis of the metastases was chorio epithelioma

Comment The chest roentgenograms of this patient illustrate the changing picture of the pulmonary metastases, their initial appearance, disappearance, and overwhelming recurrence Roentgen therapy was not a cause of the remission as it was not utilized The recurrent shower of metastases, probably from slowly growing retroperitoneal lymphatic metastases, occurred several months later as part of the terminal phase Roentgen therapy to the recurring metastatic nodules was no of avail

REVIEW OF LITERATURE

In reviewing the literature, several theories have been advanced to explain the possible etiology of this regression In 1802 Schlagenhaufer presented the first pathological description of chorio epithelioma of the testis Since then controversy has persisted as to whether this tumor is a true replica of the choriocarcinoma in the female Recently the trend toward acknowledgement has grown since further investigation has demonstrated that this tumor produces both in the male and female excessive amounts of gonadotropic hormones, gynecomastia with fibro adenomatous hyperplasia, the pregnancy changes in the pituitary gland as exemplified by the hyperplasia of the chromophobe cell, nausea and vomiting as co existing clinical symptoms, and in the male, atrophy of the seminiferous tubules of the testis, the results of excessive estrogenic hormone production

During the course of a normal pregnancy, the chorionic villi, as a result of their ability to invade blood vessels, occasionally break away and circulate as emboli in the blood stream Smorl found embolic chorionic villi in 80 per cent of normal pregnancies These emboli are destroyed by the body and absorbed The method of their necrobiosis is considered to be the result of an antisyncytial antibody or cytolysin hormone that exists in the blood stream of pregnant women Juengling and Fraenkel state that this lytic substance is not present in the female suffering with choriocarcinoma Richter transfused a woman, having pulmonary metastases from a chorio epithelioma, with whole blood from a pregnant patient and reported a cure, but attempts by other investigators to duplicate his results were unsuccessful

Saphir and Appel suggested the presence of antibody formation to explain the spontaneous remission of the Brown-Pearce carcinoma and its metastases in the rabbit They discovered that after successful testicular implantation of this tumor had produced widespread metastases, homologous intracutaneous transplantation caused a regression not only of the testicular carcinoma and the metastases, but also of the transplanted cutaneous tumor

In chorio epithelioma of the male, which is a prototype of the chorionic neoplasm in the female, consideration must be given to the fact that in the presence of chorionic tissue, antibodies or cytolysins may be produced. Their protective action could well resolve pulmonary metastases. It would be equally possible to assume that a sudden hematogenous spread of cancer cells from a slow growing retroperitoneal metastatic focus could result in an overwhelming invasion of the body thus subduing any existing antibodies.

A second theory favored by Prym is the self-destructive characteristics of the malignant chorio-epithelioma. At autopsy his case revealed extensive metastases of a choriocarcinoma. No primary lesion could be located except for a small area of scarring in one testis. Careful examination of the formation of the scar tissue indicated that this was the healed primary site of the chorio-epithelioma. Craver and Stewart, Rottino and DeBellis, have reported similar cases with the same opinions. In none of their cases was there any evidence to substantiate the possibility of an extragonadal origin of the chorio-epithelioma. Friedman and Moore discovered evidence of necrosis and scarring in eighteen of their 922 testicular tumors. In seven of these cases, the retroperitoneal metastases contained choriocarcinoma or embryonal carcinoma cells. The malignant chorionic tissue possesses strong invasive qualities, and the erosion into a blood vessel could result in a localized hemorrhage. Necrosis with eventual fibrosis and scarring would occur. The primary choriocarcinoma lesion may send out metastases before growing to any visible size. The scar of a spontaneous remission would therefore remain small and be easily overlooked. With regards to the present case report, one could postulate that the same pathological process of self destruction occurred in the pulmonary metastases. The resulting small scars would be difficult to identify at autopsy, especially if the entire lung was studded with recurrent metastases.

Moore and Friedman, in a more recent discussion of the evolution of testicular tumors, suggested that a further maturation process of the malignant chorionic tissue may occur. This would simulate the course of chorionic villi in the normal pregnancy cycle, undergoing spontaneous degeneration and residual fibrosis. This maturing process has been noticed in other tumors, and Stewart mentions two cases of malignant neuroblastoma of the adrenal which developed into the benign ganglioneuroma. This maturation growth could be applied to metastases containing chorionic tissue and explain their spontaneous regression.

McClelland described 2 cases of teratocarcinoma of the testis with pulmonary metastases. When the remaining testis of each patient was excised, a complete regression of the pulmonary metastases occurred. After several months, however, recurrent pulmonary metastases developed in both patients. Shivers and Axilrod reported a seminoma of the left testis with palpable para-aorta nodes. Following bilateral orchiectomy and intramuscular administration of stilbestrol, a 75 per cent reduction in the size of the palpable retroperitoneal nodes occurred in 2 weeks. In both reports the question of a hormonal influence arises. Can imbalance of hormonal values produce a gonadal tumor or can the growth or regression of gonadal tumors be controlled by the sex hormones. Shivers suggested that reduction of the circulating androgens, plus administration of estrogens to neutralize the adrenal androgens, might be a factor in growth inhibition of testicular tumors. Although this may be only temporary as in the cases described by McClelland, the correlation of the temporary control of breast and prostatic carcinomas by hormones should be noted. The chorio-epithelioma produces an excessive amount of gonadotrophin, a hormone of pregnancy. This hormone physiologically has the opposite effects as compared to the estrogens. Park and Lees therefore intimated that perhaps large doses of estrogens would have an adverse effect on the cells secreting the gonadotrophin and thus inhibit further growth of the tumor cells.

SUMMARY

A case of spontaneous regression of pulmonary metastases, temporary in nature, arising from a teratocarcinoma of the testis with a co-existing chorio-epithelioma, is reported. The literature has revealed four different theories regarding the possible etiology of spontaneous remission. Whether the antibody, hormonal, self-destructive, or maturation process or a combination of these can produce these regressive changes, has not yet been determined. Similar cases have probably been seen but not reported. A comprehensive analysis of these cases might lead to better evaluation and a possible means of control of these highly malignant tumors.

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EPIDERMOID CYST OF THE TESTIS

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Benign tumors constitute only two to four per cent of all neoplasms of the testis. The exact incidence of teratomas which pursue a benign course is difficult to judge, for these are potentially malignant, and are often included with those which are frankly malignant. Cairns[1] in 1926 collected a total of 47 cases of undoubted testicular dermoids in man, and since that time, less than a dozen additional cases have been added to the literature.[2-7] Of the 3 cases reported by Dockerty and Priestley, one was a pure epidermoid cyst. Kimbrough and Cook list an epidermoid cyst occurring in their series of 106 testicular tumors, but include no description. The only other mention of epidermoid cyst of the testis made in the literature are the two cited by Ewing.[8]

CASE REPORT

A 37 year old white man entered the USPHS Hospital, Baltimore, on July 28, 1953, complaining of a painless but enlarged left testis, first noticed following a blow to the left hip and lower back four months prior to hospital admission. The review of systems disclosed only the presence of a slightly productive cough of several years' duration. Past history included syphilis treated in 1947. Physical examination showed a man appearing in excellent health. The left testis was the same size as the right, but was quite firm to palpation. An apparently normal epididymis could be outlined by palpation, and a firm area which could not be transilluminated was noted in the lateral aspect of the upper pole of the testis. X-ray of the chest showed a small, round, density in the lateral segment of the right middle lobe. The hematological studies and urinalyses were within normal limits. There was no evidence of abnormal gonadotrophin excretion, and the serological test for syphilis was negative. Examination of the sputum as well as gastric and bronchial washings revealed neither malignant cells nor tubercle bacilli. On July 30, 1953, a left orchiectomy with high ligation of the spermatic cord was performed, and on September 4, 1953, an exploratory thoracotomy was done with resection of the middle lobe of the right lung.

Gross examination of the left testis showed the tunica albuginea to be taut, smooth, shiny and intact. Section revealed a round, unilocular, cystic structure two centimeters in diameter, well encapsulated by a thin wall, and entirely intratesticular. The cyst contained a soft, flaky, yellowish-white, amorphous material.

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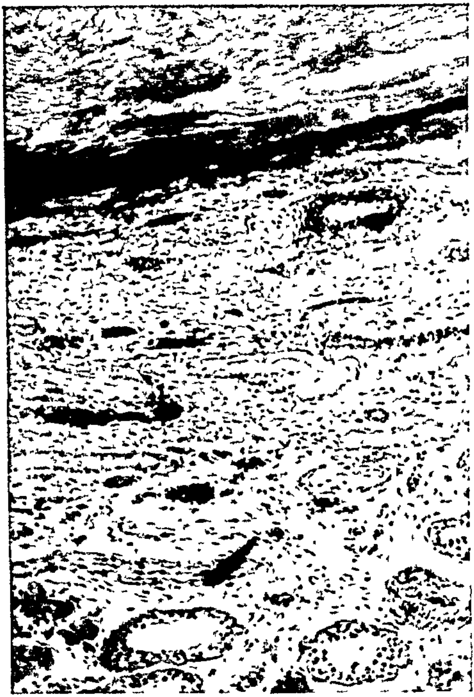

FIG. 1. Section of cyst showing wall contents and adjacent seminiferous tubules.

Microscopic examination of sections taken from many areas of the cyst wall and of its contents showed a consistent picture. The cyst wall was composed of keratin-producing, stratified squamous epithelium, several cells in thickness. This rested upon a well defined basement membrane of moderately dense fibrous tissue, beyond which were compressed and atrophic seminiferous tubules. There was no evidence of specialized epithelial structures in the cyst. Microscopic examination of the solitary lung lesion showed a chronic granuloma, morphologically resembling tuberculosis with activity.

DISCUSSION

Teratomas have long been a source of wonder. At one time, in the male, they were regarded as a repetition of the process by which Eve was born of Adam. The mode of origin of teratomas remains unknown, and the varied theories advanced in explanation have been reviewed by many writers.[9-16] Internal twin-

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ning, growth of polar bodies, proliferation of dislocated or supernumerary blastomeres, parthenogenesis of sex cells, and developmental errors in the primitive streak have all been considered. Generally speaking, these may be divided into the monogerminal and bigerminal hypotheses.

The bigerminal hypothesis maintains that there is a second independent embryonal anlage which did not reach normal body form or structure, but remains a suppressed fetus imprisoned by the tissue of the completely developed organism. Nicholson and Willis have written at length on this concept, and have pointed out that while occasional formed structures are seen, and that various tissues are found in the relationship akin to that in the complete organism, there is a total lack of axial organization and development of true somatic regions.

The monogermal hypothesis implies that in every case, the tumor arises from a totipotent germ cell from a single embryo.[17-20] The cells of the morula have the prospective potentiality to form placental chorionic cells, primordial germinal cells, and somatic cells of all three germinal layers. Normally, they split into cells with placental chorionic potentialities and cells with primordial germinal plus somatic potentialities. The latter cells then divide forming two groups of cells, the primordial germinal cells and the somatic cells. If the second cleavage occurs after the cells enter the gonad, the cells with somatic potentialities may later give rise to a primary teratoma.

Blastomeres are totipotent, and such misplaced or supernumerary pleuripotent cells may later give rise to chorio-epithelioma by the placental chorionic component, or to a triphyllomatous teratoma from the somatic component. Moreover, somatic blastomeres at the time of, or after differentiation into the three germinal layers may be displaced. Thus, somatic potentialities of one, two, or three germinal layers may be possessed, and as only somatic potentialities are possessed, no chorionic tissue will be formed.

Parthenogenesis of the vertebrate ovum is established, and the formation of a group of totipotent cells by parthenogenesis of a sex cell has been postulated. While it is difficult to state how far experimental knowledge may be transferred to man, certain data may be of value in the eventual understanding of these tumors. Frog eggs induced to develop parthenogenetically and placed in the coelomic cavity of the parent frog have produced tissue masses resembling human ovarian teratomas.[21] Rabbit embryos, whole or in part, have been transplanted to the anterior chamber of the eye and to the testis of rabbits or guinea pigs, with the formation of growths resembling teratomas.[22] This may be merely the demonstration that embryonic tissues may continue to survive and dif-

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ferentiate under abnormal circumstances. Injections of zinc chloride and zinc sulfate into the testes of roosters during the period of vernal spermatogenesis, or at any time when the injections include pituitary extract, initiate a neoplastic process beginning in the tubules immediately adjacent to parenchyma rendered necrotic by the injected material. The neoplasm takes the form of a proliferation of sheets of carcinoma-like epithelial cells which then undergo teratoid degeneration, leading ultimately to the formation of a typical adult teratoma.[23-26]

Spemann[27] has demonstrated that the orderly development of tissue of the embryo depends not upon the inherited propensities of the embryonic cells and their predestination for a particular germ layer, but rather upon the action of substances termed organizers. The development of organoid structures in teratomas suggests the influence of the embryologist's second grade and third grade organizers. Krafka[28] attributed teratomas to aberrant activity of the primary organizer with the formation of secondary embryonic axis, and explained the observed distribution frequency of teratomas as a function of the potential field of Hensen's node. However, while the influence of the secondary organizer is suggested, action of a primary organizer is very plainly lacking in that no axial arrangement is seen. Rather there is suggested by the chaotic differentiation seen that isolated cells or cell groups of the morula or blastula have escaped control of the primary organizer,[29] while the secondary organizers continue to function, thus producing the conglomeration of tissues without segmental or axial arrangement.

The subsequent degree of differentiation and development of the pleuripotent cells determine the pattern of the tumor. All germ layers may be represented in varying degrees of differentiation. However, there may be overgrowth in one germ layer at the expense of the others,[30, 31] and a tumor which was originally triphyllomatous may be seen finally as a biphylloma or a monophylloma. Similarly, one tissue component may dominate, and the others disappear. Thus, both the struma ovarii[32] and the pseudomucinous cystadenoma[33] are considered to be teratomas in which a single epithelial type has outgrown all other tissue components It is proposed that the epidermoid cyst reported represents a cyst of teratomatous origin, in which the epidermal component has outgrown and blotted out all other elements.

SUMMARY

A case of pure epidermoid cyst of the testis is described. The literature is reviewed, and it is suggested that this represents a cyst of teratomatous origin, with domination by a single tissue component

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A CYTOLOGIC EVALUATION OF THE PROSTATIC SMEAR IN CARCINOMA OF THE PROSTATE

IRWIN N. FRANK

The microscopic examination of body fluids for the presence of cancer cells is an established laboratory procedure. However, it was only as the result of the studies of Papanicolaou and his associates during the past 25 years that the method has received any recognition as a useful diagnostic aid.[1, 2] It was their work which standardized the staining technique, classification, and methods now utilized by most cytologists. At present, the vaginal smear is a routine procedure in many hospitals. Examination of sputum and bronchial aspirations is rapidly becoming more useful in the diagnosis and confirmation of bronchogenic carcinoma. The examination of ascitic fluid, pleural fluid, gastric washings, urine, and prostatic secretions has also proven of great value in the hands of some investigators and still many other body fluids are routinely examined in larger institutions.

The value of exfoliative cytology as an aid in the early diagnosis of malignancy of the male genito-urinary tract has been the subject of many controversial investigations and papers.[3-12] As a result of these studies, several of the limitations inherent in the method and those related to the anatomical region under consideration have been stressed. The time involved in reading smears, the training of personnel, difficulty in obtaining adequate material, and reports of finding diagnostic cells in only a small percentage of positive cases are all strong limiting factors. However, after routine use of the technique in our laboratory for approximately four years, we feel that these limiting factors are either not valid or can

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This study was supported in part with funds from the Dr. Henry C. Buswell Memorial and carried out in the cytological laboratory supported by the Monroe County Branch of the American Cancer Society and Rochester Health Bureau.

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be partially overcome and that the examination of prostatic secretions is definitely a useful diagnostic tool. It will be the subject of the remainder of this paper to discuss briefly the methods employed, the cell types found in prostatic secretions, the clinical statistics gathered over a three year period, and to draw a few conclusions based on the studies carried out in our laboratory.

COLLECTION AND PREPARATION OF MATERIAL

The material for examination is obtained by prostatic massage. An effort is made to avoid the seminal vesicles since fluid expressed from them dilutes the prostatic secretions and makes interpretation more difficult and the specimen less representative. The material expressed by massage is placed on a clean slide previously filmed with a thin adhering surface of albumin-glycerin. Another similar slide is placed over the first one and the two slides are pulled apart leaving a thin film of cellular material on each slide. They are then placed back to back immediately into a fixative containing equal parts of 95 per cent alcohol and ether. Immediate fixation is essential since drying results in unsatisfactory specimens However, the slides may remain in the fixative for many days prior to staining with no ill effects.

After a minimum 30 minute fixation, the slides are stained by the standard Papanicolaou procedure and mounted.[13] They are read in a systematic manner which provides for the low power examination of every microscopic field on both slides. High power and oil immersion are used to evaluate suspicious groups. The examiner then classifies the smears and sends a report to the clinician.

CLASSIFICATION OF SMEARS

The cells seen on the prostatic smear arise from any source in the genito-urinary tract which empties by patent ducts into the urethra. However, the most frequent epithelial cells seen are those from the prostate, seminal vesicles, bladder, and urethra. Seminal fluid containing many spermatozoa is not an uncommon diluting medium. Also present are polymorphonuclear leukocytes, histiocytes, occasional erythrocytes, and prostatic concretions. The latter are usually a good indication of adequate prostatic representation.

Classification of prostatic smears depends upon the amount and source of the material expressed, and upon the therapy the patient has received. Therefore it is not unusual that material from the same patient may be classified differently from time to time if it is representative of different parts of the prostate or if the cells have been modified by estrogen therapy. With due consideration to these factors and ample evidence that the cells seen are representative of prostatic material, the smears are classified into one of the five categories represented in table 1 "Quantity not sufficient" and "unsatisfactory specimen" reports are sent to the clinician in cases of inadequate material and poorly prepared or unrepresentative specimens.

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[13] Papanicolaou, G N and Traut, H F Diagnosis of Uterine Cancer by the Vaginal Smear New York Commonwealth Fund, 1943.

TABLE 1. *Cytologic classification of smears*

Class I	Absence of abnormal or atypical cells.
Class II	Atypical cells present but without abnormal features.
Class III	Cells with abnormal features but not sufficiently pathognomonic.
Class IV	Large number of pathognomonic cells and cell clusters.
Class V	Large number of conclusive cells and cell clusters.

Therefore, a Class I report implies that the material examined is adequate in amount and contains what is believed to be representative, normal prostatic secretion. Prostatic inflammation, metaplasia, and slight increase in nuclear activity are present in most cases reported as Class II. It is the Class III or suspicious grading which should alert the clinician to re-evaluate the case and to obtain a repeat specimen. This classification represents the most difficult of cytologic interpretations. In this group lie the specimens which show small numbers of abnormal cells, and borderline suspicious cellular characteristics. These smears require careful, time-consuming scrutiny and, frequently, examination with maximum magnification. Class IV reports indicate that the material seen is suggestive of malignancy and Class V has a similar connotation with the difference being one of the conviction of the examiner as based upon the amount of abnormal material and the extreme cellular changes present.

While a Class V report is indicative of malignancy, it offers no evidence of the extent of growth. This can be demonstrated only by obtaining further clinical, laboratory and radiological evidence. Therefore, Class V does not necessarily mean a more invasive or more malignant lesion than Class IV but may only indicate that a larger number of malignant cells have been mechanically expressed during massage.

CYTOLOGIC CRITERIA FOR MALIGNANCY

In differentiating malignant cells from those seen in the normal or benign smear certain criteria have been established which are outlined in table 2. It is rarely the case that all are present and usually only two or three criteria are seen in any one case. It has been our experience that the presence of large nucleoli and cast-like cell groupings are the most reliable and most frequently encountered characteristics present in specimens obtained from the prostate harboring a malignancy.

TABLE 2. *Cytologic criteria of malignancy*

1. Variation in size and shape of nuclei.
2. Hyperchromatism.
3. Crowding of cells and overlapping of nuclei (in sheets).
4. Bizarre, irregular nuclei.
5. Chromatin stippling and patches.
6. Single large or multiple nucleoli with altered nucleoli-nuclear ratio.
7. Mitotic figures (rarely seen).
8. Cast-like cell groupings.

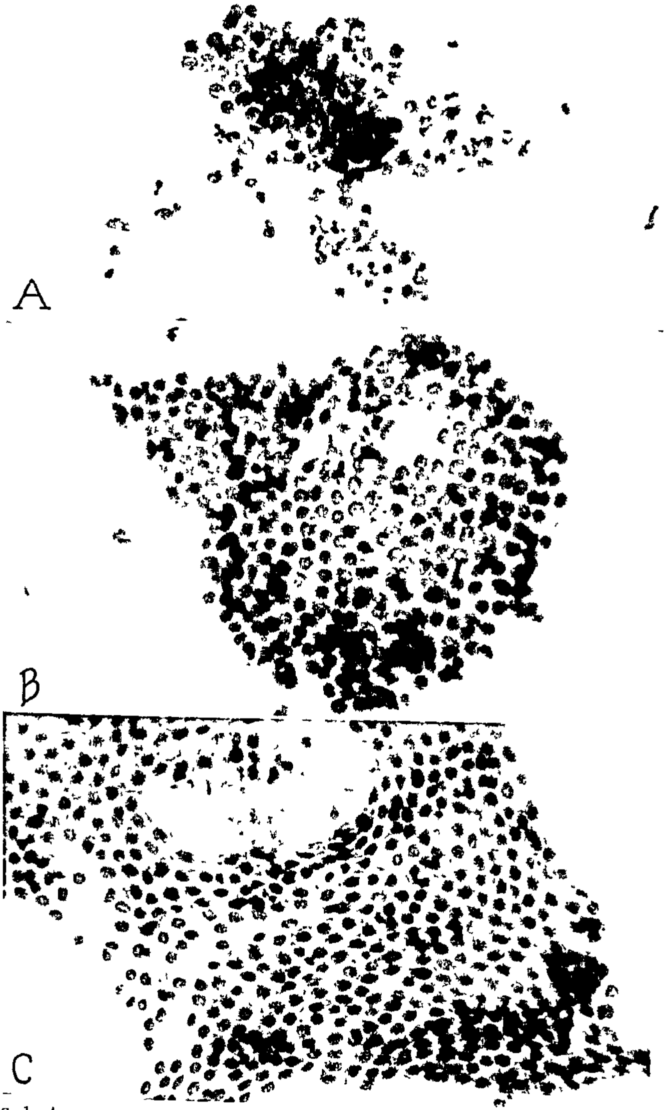

FIG. 1. *A*, group of columnar cells in prostatic secretion (×430). *B*, sheet of columnar cells from hypertrophied prostate (×430). *C*, large desquamated sheet of columnar cells with honey-combed structure (×430).

CHARACTERISTIC CELL TYPES

Normal and benign prostatic hypertrophy. The columnar cells expressed by massage of the normal and the hypertrophied gland are present singly, in loose groups or in desquamated sheets (fig. 1). The well-preserved nuclei (6 microns) are pale staining with fine stippling and have occasional or rare small nucleoli. There is no crowding and the nuclear outline is distinct. Uniformity of size and shape is the rule and variations usually indicate degrees of atypia or abnormality. Scant material is expressed from the prostate of the younger man while an increase in exfoliated cells characterizes benign prostatic hypertrophy. Also in the latter condition, one more frequently notes desquamated sheets with well spaced nuclei, ample eosinophilic cytoplasm, and a slight increase in nuclear size. In many instances, the columnar cells seen represent degenerated forms with loss of cytoplasm and only dark, uniformly staining, single, basophilic nuclei remaining. This degeneration probably represents desquamation prior to massage and mechanical expression. Other epithelial cells seen are those lining the urethra, bladder and seminal vesicles. These are squamous, transitional and columnar cells. The seminal vesicle columnars are indistinguishable from those expressed from the prostate except in cases in which pigment is recognized in the cytoplasm indicating seminal vesicle origin or when the total picture is one of seminal fluid.

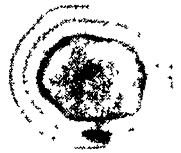

FIG. 2. Prostatic concretion (×430).

Cells of nonepithelial origin are also seen in the smear. Erythrocytes, leukocytes, and histiocytes frequently are encountered. The histiocytes are most often characterized by their bean-shaped, indented, hypochromic nucleus and finely vacuolated, foamy appearing, pale staining cytoplasm. This cell type may be seen in giant cell forms and with considerable variation. Degenerated leukocytes, debris, sperm and pigment may be seen within the cytoplasm of the histiocyte offering ample evidence of the phagocytic properties of the cell.

The only noncellular element of importance in the smear is the prostatic concretion. As previously mentioned, corpora amylacea (fig. 2) are usually an indication of the source of the massaged specimen and thus may play a role in determining adequacy of representation.

The material expressed from the normal or hypertrophied prostate with superimposed infection is composed of the elements described above. However, there usually is a marked increase in the number of polymorphonuclear leukocytes and histiocytes (fig. 3, *A*). Inflammatory epithelial changes also occur and are illus-

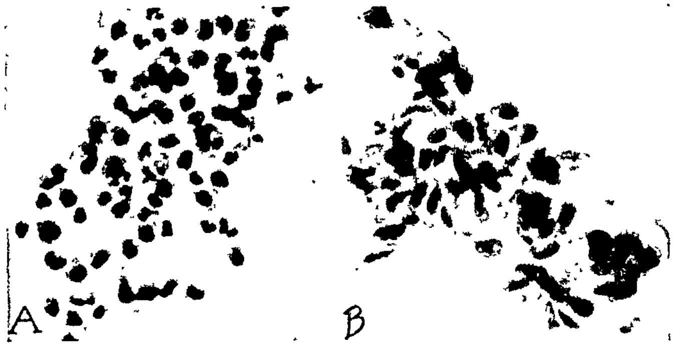

FIG. 3. *A*, loose group of polymorphonuclear leukocytes and histiocytes (×430). *B*, columnar cells showing inflammatory changes (×430).

trated in figure 3, *B*. These cells show elongation of nuclei, moderate increase in activity, and ample cytoplasm. Very frequently, this inflammatory picture results in a Class II report.

Seminal fluid. Many spermatozoa and seminal fluid provide a diluting medium which may make cytologic interpretation difficult or impossible. However, malignant cells may be found within this material and careful screening is essential. A cell of considerable interest, which is often found in the seminal fluid of men over fifty years of age, is the histiocyte with sperm (fig. 4). This cell represents a large histiocyte, usually with two nuclei, which has engulfed varying numbers of mature spermatozoa and, occasionally, yellow seminal vesicle pigment. Direct organ smears of the seminal vesicles revealed the presence of very bizarre cells. Occasionally one of these cells is expressed on massage and may provide considerable difficulty in interpretation if one is not familiar with its origin. These bizarre cells are characterized by large, irregular, hyperchromatic, coal-like nuclei with intranuclear areas resembling nucleoli (fig. 5). Such a cell may be misinterpreted as being malignant. However, they are seldom present in the massaged specimen and when seen, they occasionally contain a small amount of yellow seminal vesicle pigment which may aid in deciding upon their origin. In our experience, they have provided no real difficulty but one should be aware of their existence.

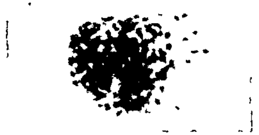

FIG. 4. Single histiocyte with engulfed spermatozoa (×430).

Carcinoma. Any or all of the cellular and noncellular elements described above may be present in the material expressed by massaging the prostate of a patient with a carcinoma of that gland. In addition, varying numbers of cells are present

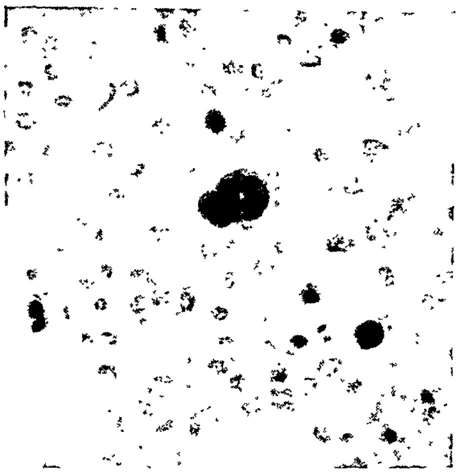

FIG. 5

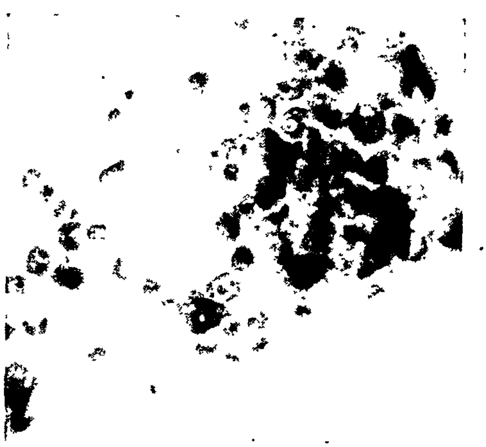

FIG. 6

FIG. 5. Single bizarre cell from seminal vesicle (×430).

FIG. 6. Group of malignant cells demonstrating hyperchromatism, variation in size and shape of nuclei, crowding and large prominent nucleoli (×430).

which are abnormal as determined by the criteria outlined in table 2. The malignant cells most frequently are seen in sheets or in loose groups with variation in size and shape of nuclei, crowding, large multiple nucleoli and hyperchromatism (fig. 6). However, the presence of cast-like structures (fig. 7) in a specimen should immediately arouse suspicion even if the nuclei appear to be uniform in size, and crowding is not marked. Higher magnification usually reveals the presence of large nucleoli in the cells around the periphery of the cast where detail is best preserved. These configurations may represent growth of malignant cells into acini with resultant cast formation and breaking off and expression by massage.

Occasionally, single malignant cells are present and may provide difficulty in recognition unless careful screening is carried out. The amount of difficulty encountered is proportional to the degree of abnormality of the individual cells. The most bizarre and grossly malignant cells seen have been found in cases where material from a bladder carcinoma has appeared in the massaged specimen (fig. 8).

Hormonal therapy. Marked histologic changes are evident in the prostate which has been subjected to estrogen therapy. These changes are reflected in the cells desquamated from such a gland. Approximately three weeks after a patient with carcinoma of the prostate has taken such medication, pronounced cytologic changes are noted which are considered to be characteristic of response to estrogen therapy. Profuse desquamation of large squamous cells, alteration of malignant cells, and the presence of "glycogenic cells" are the characteristic changes resulting from continued estrogen therapy (fig. 9). The squamous cells are normal appearing but are greatly increased in number as compared to specimens from the untreated gland wherein squamous cells make up a small part of the total cell population.

"Altered" malignant cells are characterized by giant cell formation, loss of nuclear detail with bland degenerated appearance, and occasionally increased cytoplasm. The loss of nuclear detail present with estrogen response increases the

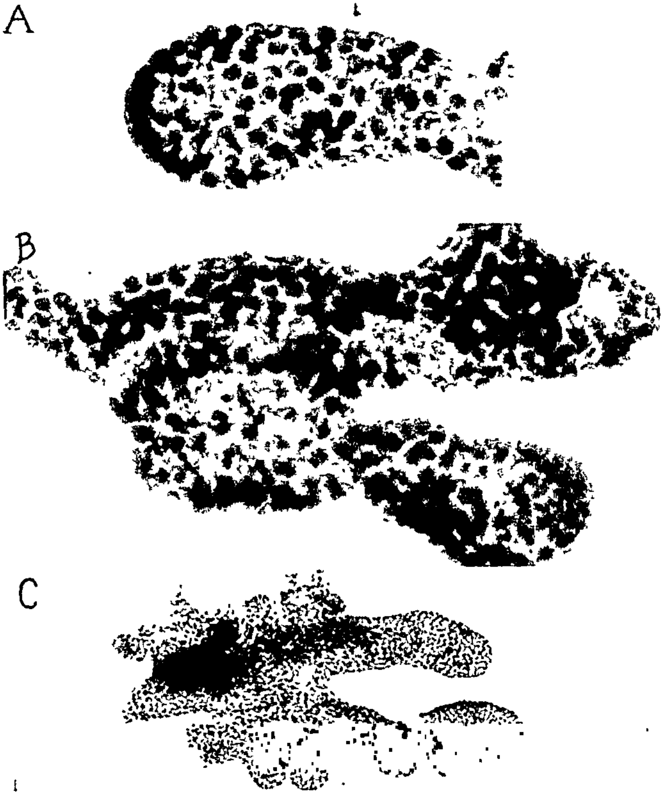

Fig. 7. *A*, small malignant cast-like structure with minimal anisonucleosis (×430). *B*, malignant cast with marked crowding (×430). *C*, large malignant cast (×100).

difficulty in interpretation of specimens obtained from massage of the gland subjected to estrogen. If a patient is followed with smears during the course of therapy, the gradual changes may be noted and malignant cells are recognized with varying degrees of alteration. However, if a patient is seen for the first time after he has undergone a prolonged period of successful hormone therapy, the value of the smear for diagnosis is greatly diminished. The alteration in malignant cells with loss of the criteria previously outlined, and the gradual disappearance of malignant cells entirely, as frequently occurs, make interpretation of the underlying changes impossible. One can only state that the picture is one of estrogen response. It is for this reason that smears should be obtained before estrogen therapy has been started.

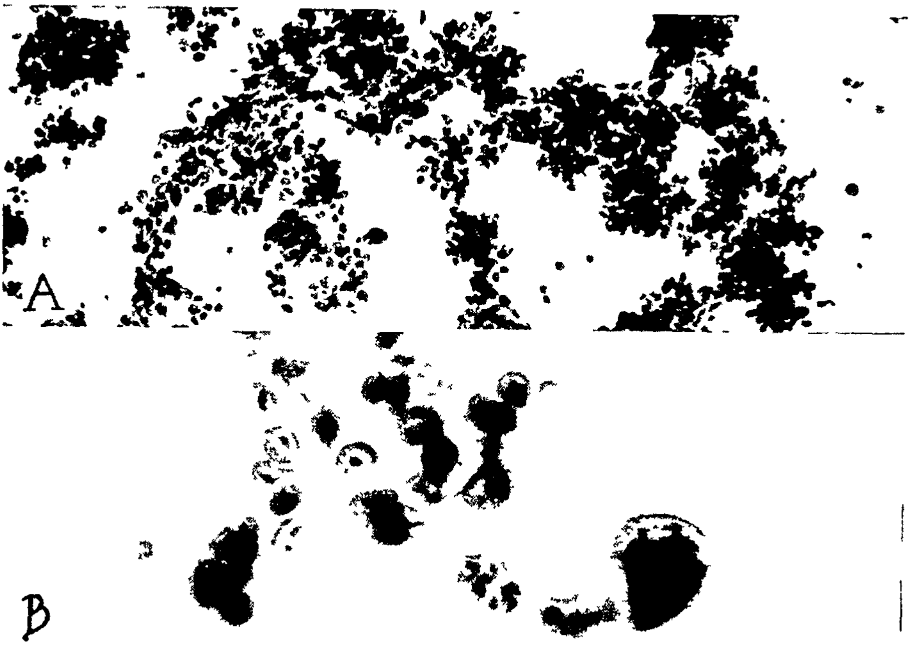

FIG. 8 *A*, sheets of malignant cells from bladder carcinoma (×100) *B*, loose group of bizarre malignant cells from bladder carcinoma showing marked anisonucleosis and prominent nucleoli (×430).

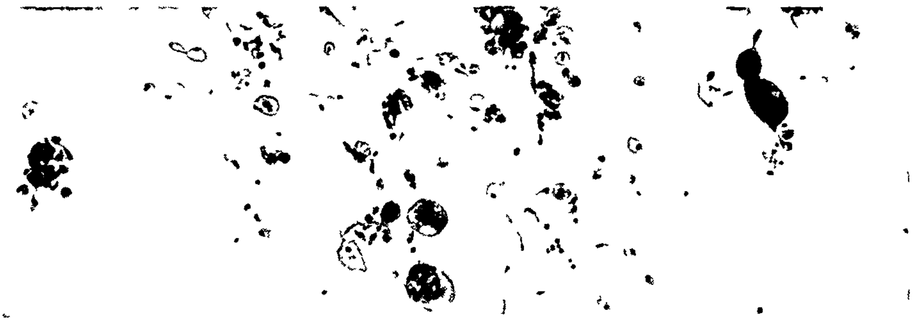

FIG 9. Estrogen effect demonstrating squamous cells, "glycogenic cells," and malignant cells altered by therapy (×100).

FIG. 10. Single "glycogenic cell" and two small squamous cells (×430).

TABLE 3 *Breakdown of suspicious (III) and positive (IV&V) prostatic smears from 1,052 new patients seen at Strong Memorial Hospital from September 1949-September 1952*

	No of Cases	% of Total Cases (1,052)	Histolog or Clinically Proven Ca	Histolog Proven Benign	Clinical Data Insufficient or Absent	Minimal % Proven Ca*
III	33	3 13	18	4	11	54 5
IV	89	8 46	73	5	11	82 0
V	16	1 52	16	0	0	100 0
Total	138	13 11	107	9	22	—

* % Does not include positives in insufficient data group

"Glycogenic cells," as described by Dr. Hannah Peters[14], are the most characteristic cytologic change noted in cases of responsive estrogen therapy (fig. 10). It has been our experience that they have only been seen in the smears of patients who have had such medication. The cell, which has its origin in metaplastic areas of the prostate, is distinct in its features and easily recognizable The cell outline is clearly delineated by a thin, darkly staining, round or oval membrane giving the cell an average diameter of approximately 26 microns Within the cell border is a narrow clear area which encircles a denser, pink staining, homogeneous, glycogen containing mass of cytoplasm. The eccentric oval nucleus (8 by 4 microns) is usually dark and without any nuclear detail.

It is of interest to note that the appearance of the cytologic picture described above often coincides with the clinical changes characteristic of successful estrogen therapy. Cessation of therapy is accompanied by disappearance of "glycogenic cells" and the eventual return of unaltered malignant cells

CLINICAL DATA

In the period from September 1949 to September 1952, we examined prostatic smears from 2,198 patients seen primarily by the urologic service in Strong Memorial Hospital. Of these, 1,052 of the patients were seen for the first time and the remainder of the smears were obtained upon repeat visits In all but a few cases, the patients were over fifty years of age Two smears were prepared from each massaged specimen and these were examined and classified as previously described For statistical purposes, only the findings on the new patients will be discussed at this time The breakdown of the classification of these 1,052 cases is illustrated in table 3 Eight case findings were present in this series and represent positive smears obtained on patients who were not suspected clinically of having carcinoma of the prostate. In these instances histologic sections prepared from punch biopsy, surgical, or autopsy tissue later confirmed the positive cytologic findings Negative histologic sections were obtained on five patients on whom Class IV smears had been reported (false positive), while positive histologic sections resulted from a similar number of cases wherein the cytologic reports were negative (false negatives)

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[14] Peters, H and Benjamin, J A The prostatic smear Cell changes after estrogen therapy. Surg Gynec & Obst , 91: 660 668, 1950

DISCUSSION

From these figures one may conclude that a positive cytologic report (Class IV and V) is correlated with at least an 85 per cent accuracy and that suspicious reports (Class III) warrant further clinical studies and repeat massage in an effort to rule out the presence of a prostatic malignancy. These results correspond favorably with a previously reported study in which smears prepared on 100 cases of proven carcinoma of the prostate yielded 88 per cent cytologically positive reports. Of the remaining twelve cases, seven were reported as suspicious of malignancy.[11]

It is our belief that the one single factor which is of greatest importance in making the prostatic smear an applicable diagnostic aid is the close co-operation between the clinician and the cytologist. This implies an attempt to make each specimen adequate in material and properly fixed without drying; to repeat smears on all cytologic Class III and clinically suspicious cases; to obtain follow-ups on patients with reports of the histological, surgical and therapeutic procedures carried out; to study specimens prior to estrogen therapy; and to have a mutual understanding of terminology and implications of each classification. It is the cytologist's responsibility to become acquainted with one standardized staining procedure, to examine direct organ smears when possible, and to give simplified, accurate reports within a short time after he receives the specimen.

SUMMARY

The microscopic examination of material expressed from the prostate by digital massage is of value in determining the presence of a carcinoma in that gland. The secretions obtained in this manner are fixed, stained, and examined by a standardized procedure. Cytologic criteria of malignancy, a fixed classification system, and characteristic cell types are discussed. A three year survey of prostatic smears from 1,052 patients revealed that a positive cytologic report was correlated with at least an 85 per cent accuracy. A breakdown of the suspicious and positive classifications is tabulated with further information regarding case findings, false positives, and false negatives. Close co-operation between the clinician and the cytologist is stressed. It is concluded that the prostatic smear offers a reliable adjunct to the diagnosis of prostatic carcinoma, a means of detecting an occasional case which is clinically unsuspected, and a technique suitable for assaying estrogen response.

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PROSTATIC CANCER VI. MORTALITY RATE OF RADICAL SURGERY FOR ADENOCARCINOMA OF THE PROSTATE

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As the scope of operative technique widens, in any historical period, evaluation of the efficacy of and mortality from these methods must properly be made. Such scrutiny is highly desirable today, when extended surgical dissections are being increasingly applied to eradication or palliation of certain malignant growths

Those malignant tumors of most frequent incidence and which most often produce fatal outcome are of greatest concern to surgeons. Among these neoplasms, prostatic cancer assumes a prominent position. Of the intrinsic adenocarcinomas directly causative of death in men in the United States in 1950, those of the prostate are numerically second only to gastric cancer. In 1935, prostatic cancer led to the death of 12 men of each 100,000 of the U. S. male population, by 1918, this mortality rate had risen to 15.† These figures reflect a progressive increase in death rate from this cancer concomitant with the rising proportion of aging individuals within the population.

Prostatic cancer belongs within the group of malignancies for which radical surgery is a feasible form of therapy.

If one considers the chronological development of any type of cancer surgery, it becomes obvious that there is a trial, error and improvement phase through which new operations must pass prior to the time at which they become acceptable systems of treatment. For example, one of the first radical surgical procedures conceived, as a curative measure, was the Halsted operation for carcinoma of the breast, reported in 1894.[1, 2] It is recalled that Halsted's operation did not at first receive wide acceptance, initially, the operative mortality rate was not low.[3] Nevertheless, the Halsted procedure has, with certain modifications, stood the test of time and has emerged as a preferred method of treatment for many breast cancers, particularly those to which the principles for case selection of McDonald, Haagensen and Stout are closely applied.[4] [5]

Whether or not radical surgery, such as pelvic exenteration, will similarly emerge as a useful and advocated modality for the cure or control of cancer remains to be seen. Suffice it to state that pelvic exenteration, whether per-

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† Data provided by the Statistical Division of the American Cancer Society, 47 Beaver Street, New York, N Y.

[1] Halsted, W S · Johns Hopkins Hosp Report, 4: 1, 1894

[2] Halsted, W. S Ann Surg., 46: 1, 1907

[3] Lewis, D and Rienhoff, W F.: Ann Surg , 95: 336, 1932.

[4] Haagensen, C D and Stout, A. P Ann Surg , 118: 859, 1943

[5] McDonald, J J , Haagensen, C. D. and Stout, A. P.· Surg , 34: 521, 1953. (See abstr. by Urban, J A , Cancer, 7: 415, 1954)

formed for cancer of the cervix, cancer of the bladder or cancer of other pelvic organs, rests on the level of investigative clinical surgery at present. In any opinion of this work, Brunschwig's 18 per cent mortality which occurred within 30 days after operation in 302 completely unselected cases of cervical cancer must be considered.[6] Nonetheless it is clear that pelvic exenteration has benefited many individuals who otherwise would have been destined for an earlier death.[7]

Radical surgery, however extensive, often falls short of curing many types of tumors, despite low operative mortality.[8, 9] Pneumonectomy for carcinoma of the lung[10, 11] and total pancreatectomy for carcinoma of the pancreas[12-14] probably belong in this category. In both instances it is likely that the immediate postoperative deaths exceed the number of cases cured.

In view of such patently discouraging records for nonurological tumors, urologists have been understandably cautious in undertaking radical surgery for cancer of the genito-urinary tract. In order to ascertain whether or not such caution has exceeded normally prudent restraint one must examine the results of surgical treatment of prostatic cancer.

Adenocarcinoma of the prostate gland was once thought to be a rare lesion.[15] It is now known to be a common disease and a frequent cause of death in the aging male.[16-18] A well-conceived, effective operation for the ablation of prostatic cancer was described by Young in 1905.[19] As Jewett emphasized, Young's operation was not hastily contrived, but was instead based upon the known morbid anatomy and pathogenesis of the disease.[20] Yet, Young's operation has not been widely used by genito-urinary surgeons with the exception of those trained in his clinic. As recently as 1950, radical perineal prostatectomy was described as "practically abandoned in Europe."[21]

The reasons for reluctance in accepting total prostatectomy for cancer seem to center, in actual practice, upon the undesirable postoperative sequelae, of which incontinence (about 8 per cent of the operated cases)[16] is the most disconcerting. The postoperative mortality rates for prostatic cancer surgery, however, could not possibly be a reasonable deterrent to the conscientious cancer surgeon. In a large series of radical perineal prostatectomies, Young reported a

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[11] Rienhoff, W. F.: Dis. Chest, **17**: 33, 1950.

[12] Brunschwig, A.: Cancer, **3**: 624, 1950.

[13] Parsons, W. B.: Bull. N. Y. Acad. Med., **27**: 339, 1951.

[14] Catell, R. B. and Warren, K. W.: Surgery of the Pancreas. Philadelphia: W. B. Saunders Co., 1953.

[15] Rich, A. R.: J. Urol., **33**: 215, 1935.

[16] Medical Forum on "Results of Total Prostatectomy", Modern Med., **22**: 136 et. seq. (March 1) 1954.

[17] Marshall, V. F. and Whitmore, W. F., Jr.: J. Am. Geriat. Soc., **1**: 190, 1953.

[18] Edwards, C. N., Steinthorsson, E. and Nicholson, D.: Cancer, **6**: 531, 1953.

[19] Young, H. H.: Johns Hopkins Hosp. Bull., **16**: 315, 1905.

[20] Jewett, H. J.: J. Urol., **61**: 277, 1949.

[21] Westerborn, A.: Surg., Gynec. & Obst., **91**: 751, 1950.

mortality rate of 16 6 per cent [22] An extension of this group by Jewett reveale a mortality rate of 6 3 per cent [20] Colston, at the same institution, has pe sonally performed 98 radical perineal prostatectomies without a fatality [23] It notable that many of the operations included in these published accounts we performed before the advent of sulfonamide therapy, the antibiotic drugs blood banks During that same era, Belt reported a mortality rate of only per cent for radical perineal prostatectomy [24]

The 28 per cent 10 year cure rate from total prostatectomy cited by the Johns Hopkins group would be sufficient to encourage broader use of this surgical approach [20] Both low surgical mortality rate and also comparatively high cure rate provide adequate incentive and reward for the surgeon who determines to achieve proficient performance of this operation

It seems worthwhile to add to this surgical record the fact that 52 radical prostatectomies have been performed at the Francis Delafield Hospital from March 1951–July 1953 One operative death has occurred, due to anesthesia, a mortality rate of 1 9 per cent It is significant that the vast majority of these operations were performed by the resident staff Suitable training can reduce the operation to a short, relatively innocuous surgical exercise.

In light of these briefly outlined results, we recommend that total prostatovesiculectomy be given wider use as a worthwhile form of cancer surgery.

SUMMARY

The necessity for a sober consideration of surgical mortality rates incurred by extended operations for ablation of cancer is cited

The prominent position occupied by prostatic cancer as a cause of death in the aging male is emphasized

The development of certain important radical cancer operations is traced through the early stages of questionable value to the point of general usage

Low mortality rates resulting from total prostatectomy are mentioned

An additional 52 cases of radical prostatectomy with one death, performed mainly by the resident staff of the Francis Delafield Hospital, is added to the record

[22] Young, H H and Davis, D M Young's Practice of Urology Philadelphia W B Saunders Co , 1926

[23] Colston, J A C Personal communication, April 5, 1954

[24] Belt, Elmer J Urol , 48 287, 1942

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PROGRESS IN PERINEAL PROSTATECTOMY: RESULTS IN 2050 CONSECUTIVE PATIENTS

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> "Perfection is attained by slow degrees;
> It requires the hands of time."
>
> —Voltaire

Whether perfection is attainable in any field of human endeavor is debated by the sages. No one, however, questions that manifold imperfections are inherent in each and every surgical procedure. Therefore, in all deference due the illustrious Voltaire, and referring specifically to the field of surgery, one is justified in paraphrasing the foregoing dictum to read, "Perfection is *approached* by slow degrees."

A survey of the prostatic surgical literature of the past 20 years has revealed no reported analysis of perineal prostatectomy results in large series. In that just half a century has elapsed since the debut of perineal prostatectomy in the columns of the *Journal of the American Medical Association* by Young[1] and Goodfellow,[2] a brief review of the developments which have transformed a blind, traumatizing evulsion into a procedure of precision, together with a discussion of present-day mortality, complications, convalescence, and functional results, seems to be fitting at this time. It is doubtful whether the laity (or even the profession, in its entirety) fully realizes what a benign procedure perineal prostatectomy has come to be.

It is by no means our purpose to advocate any one technique to the exclusion of others, or to revive the "perennial" controversy. Each method has its place and its skilled proponents who have achieved good results. The interests of the patient are best served by careful selection of cases, in clinics where skill by any route is available. We do believe, however, that the advantages of the perineal route are not generally recognized.

Perineal prostatectomy today, under innocuous (caudal) anesthesia, offers opportunity for painless, deliberate, precise, anatomic dissection, clear visualization, accurate hemostasis, and plastic closure with normal anatomic restoration. Following this technique, uneventful convalescence, with per primam healing, minimum hospitalization and excellent functional results is the rule rather than the exception. In brief, the prognosis, with respect to hazard and late results, following prostatectomy in the aged and debilitated has come to compare favorably with that following appendectomy in the young and robust.

Read at annual meeting, American Urological Association, New York, N. Y. June 3, 1954.

[1] Young, Hugh: Conservative perineal prostatectomy, a presentation of instruments and technic. J.A.M.A., **41:** 999–1009, 1903.

[2] Goodfellow, George: Prostatectomy in general especially by the perineal route. J.A.M.A., **43:** 1448–1450, 1904.

The various contributory factors responsible for this dramatic change, permitting plastic closure and the approach to perfection in technique, include better methods of anesthesia, hemostasis and antisepsis, also new and improved instruments. Continuous caudal anesthesia, introduced for perineal prostatectomy by Davis and Lee[3] eliminates the necessity for haste, permitting time for meticulous care in suture ligation of bleeding points. The hemostatic traction bag described by Davis[4] and now employed only during the operation, is an added factor in providing clear visualization. The antibiotics have been spectacularly helpful in promoting per primam wound healing, to the end that dismissal on the eighth postoperative day, perineum dry and urinary control satisfactory, is not unusual.

The most important factor of all, however, has been the increasing lay enlightenment, brought about by popular magazine articles, reputable medical newspaper columnists, medical society publicity programs, and, particularly, by a program of persistent, blatant, radio advertisement of a sham prostate cure, designed to deceive and defraud, but having actually and inadvertently rendered a genuine public service. "Prostate," no longer taboo, is now regarded as a fit subject for parlor conversation, people have become "prostate conscious", and we urologists have become respectable. The profession and the laity as well have come to recognize the hazard of delay, to the end that we now seldom see the midnight distended bladder, and uremic mental disorientation. Prolonged preliminary bladder drainage has become the exception rather than the rule. After an office examination and diagnosis, patients are frequently admitted for vasectomy and functional tests the first day, and operation the second.

The opinion here expressed, however, is by no means to be construed as blanket approval of routine omission of preliminary drainage, the necessity for which will always obtain with cardio-renal disorders, and other lesions, as determined by judgment.

A complete review of the evolution of perineal prostatectomy, giving credit to the many who have contributed, would not be germane to the purpose of this paper. According to Hamer,[5] "the published record indicates that perineal prostatectomy was first performed by Watson in 1889, Wishard in 1890 and Goodfellow in 1891," each without the knowledge of the other. Goodfellow, who in 1904 reported a series of 73 operations, is credited with being the first to make a success of perineal prostatectomy in America. It was Hugh Young, however, who played the major role in the development of the perineal approach, even though, by his own words, his first prostatectomy was not until 1898, and this by the suprapubic route. Young's[1] original paper appeared in 1903 describing his technique of perineal dissection, and also his perineal prostatic tractor and other special instruments. These instruments, supplemented to some extent, are still in use today, and his technique, although somewhat modified, remains essentially the same in principle. Gibson's[6] contribution, describing plastic closure of the vesical neck, prostatic capsule, and perineal incision without drainage (excepting a retained urethral catheter), and placing emphasis upon meticulous hemastasis, is an important milestone.

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[3] Davis, E. and Lee, L. W. Perineal prostatectomy under continuous caudal anesthesia. J. A. M. A., **130**: 925–926, 1946.

[4] Davis, Edwin. Distensible bag for hemostasis and drainage following perineal prostatectomy. J. Urol., *18*: 201–210, 1927.

[5] Hamer, H. G. Short sketches of the work of eminent Western urologists. J. Urol., **22**: 593–602, 1929.

SELECTION OF ROUTE

Henline[7] expressed a sane and unprejudiced viewpoint in stating, "surgical diseases of the prostate present so many variations that no one surgical procedure will obtain the best results in all cases." Of the three available routes of approach, the suprapubic (or retropubic), the perineal and the transurethral, each has its proponents and its critics; each its advantages and disadvantages. In an analysis of opinions expressed in personal communications from 100 impartially selected American urologists of reputation and achievement there were eight resection extremists and, curiously, exactly the same number declining to avail themselves of the advantages offered by the transurethral route in selected cases. Each of these small minorities may be judged precisely as unyielding and complacent as the other. The remaining 84 per cent preferred to fit the operation to the patient, rather than the patient to the surgeon. This is as it should be. It seems that the decision should depend chiefly upon 1) the size of the obstructing prostate, 2) evidence of malignancy, and 3) to a lesser degree, upon the specialized skill of the surgeon. In cases of balanced decision, we allow ourselves to be influenced by the wishes or prejudices of the patient, after he has been carefully briefed as to the advantages and disadvantages of each method. In case of obstinate insistence upon a procedure which we view as contra-indicated, we avail ourselves of the surgeon's one and only inherent right which may not be legis lated away—polite declination. Only very rarely, however, has this been necessary. It is not our purpose to prolong the "perennial" controversy, or to discredit any method, but merely to urge flexibility upon the part of the surgeon and individualization of the patient. As evidence of our appreciation of the advantages offered by the transurethral route in selected cases, we submit that we personally have performed more than 900 transurethral resections. A substantial percentage of these resections, however, was for advanced prostatic carcinoma.

Assuming prostatic surgical indication (a discussion of which is not included within the province of this paper), we are guided by the following criteria and findings in the selection of route.

- Perineal
    - Moderate-to-large benign hyperplasia
    - Early intracapsular carcinoma, without demonstrable metastases
    - Prostatic calcification
- Suprapubic
    - Moderate-to-large benign hyperplasia accompanied by: Ankylosis of

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[6] Gibson, T. E.: Improvements in perineal prostatectomy permitting primary wound closure and healing without drainage. Surg. Gynec. Obst., 47: 531–539, 1928.

[7] Henline, R. B.: The surgical treatment of prostatic disease. J.A.M.A., 117: 2030–2034, 1941.

hips interfering with lithotomy position; perineal scar tissue; massive intravesical hemorrhage; impassable urethral stricture

Transurethral
  Small benign hyperplasia
  Median prostatic bar
  Mercier's bar
  Advanced prostatic carcinoma

In the borderline group, our rule is to choose the perineal rather than the transurethral route. We do so because it is our experience that perineal enucleation under caudal anesthesia, followed by plastic closure, is less of an ordeal than transurethral resection (in our hands), is followed by a smoother, easier convalescence (without the secondary hemorrhage hazard), and offers better assurance of complete and lasting symptomatic relief. Unprejudiced opinions as to relative ease of convalescence, repeatedly volunteered by ward nurses, represent the ultimate in reliability, and would seem to establish the authenticity of this statement.

PREOPERATIVE TREATMENT

In addition to routine laboratory tests and complete physical examination, with such medical consultation as may be indicated, our routine preoperative preparation consists essentially of nonprotein nitrogen determination, roentgenological study, vasectomy and cystoscopic examination. The last, however, we occasionally omit if diagnosis is definitely established. Patients with residual urine in small amount, with normal temperature and good appetite, with normal nonprotein nitrogen, and without cardiac or other medical contra-indication, may be operated upon without delay. Residual urine in large amount, however, and/or elevated nonprotein nitrogen, call for caution. Preoperative treatment then must include forced fluids and bladder drainage, either by retention catheter or via the suprapubic route, continued for days, weeks or even many months, insistently and inexorably carried out for as long as may be necessary, regardless of urging to the contrary by patient or relatives. Simply stated, and assuming no evidence of circulatory disorder, our greenlight criteria consist essentially of nonprotein nitrogen below 40 mg., normal temperature and good appetite.

ANESTHESIA

Specifications of the ideal method of anesthesia include safety, efficiency, freedom from sequelae, ease of administration and flexibility of duration. Such methods are available today. The sane and conservative surgeon has long since discarded the speed mania, and has substituted therefore deliberateness in dissection and hemostasis. Although sacrocaudal block gave satisfactory results over a period of many years, in 1946 we substituted continuous caudal anesthesia, requiring one needle only, instead of seven, and permitting prolongation if necessary. For uniformity in results and freedom from reactions, we are delighted with cyclaine,* 0.5 per cent, recently adopted for this purpose. The initial dosage of 80 cc, which usually suffices, may be supplemented if necessary.

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* Sharp and Dohme's trade name for hexylcaine.

The use of this drug for caudal block and other purposes has been described by Lee, Davis, and Barmore.[8]

SURGICAL TECHNIQUE

Since the average reader is interested in survival of the patient and late functional results, rather than in surgical technique, a detailed description of the latter would not be here appropriate. Moreover, Young's[9] classic descriptions of the perineal approach, beautifully illustrated by Didusch, are not to be duplicated (much less improved upon), and are readily available in various publications, in addition to *Young's Practice of Urology.*

CONVALESCENCE

Having been subjected merely to innocuous, nerve block anesthesia, and negligible blood-loss, the average patient leaves the operating room in the same condition as upon entering. So-called surgical shock, which too often is a misnomer, and a manifestation of concealed hemorrhage, we do not see. Excepting the ever-possible, unforeseen complication, a discussion of which follows, routine, smooth and uneventful convalescence may reasonably be expected.

The postoperative discomfort experienced by the perineal prostatectomy patient we believe to be distinctly less than following the suprapubic or transurethral approach.

Adynamic ileus, as with other perineal procedures, and in marked contrast with the frequency of this complication following abdominal operations, is conspicuously rare. As long ago as 1889 Watson[10] wrote, "Clinically the perineal operations are the safest."

Ambulation is routinely started on the first or second postoperative day.

Wound healing. Per primam union is now the rule rather than the exception. Subcutaneous suppuration, with breaking down of the incision, followed by the slow, tedious process of separation of slough and healing by granulation, is a thing of the past. Factors mainly responsible for the elimination of wound infection include more careful surgical technique, better knowledge of nutrition, and, particularly, the specific antibiotics and the sulfonamides. Following removal of retention catheter, perineal sutures and rubber wick on the seventh postoperative day, perineal urinary drainage, even in fractional amounts, is decidedly the exception. By contrast the incidence of wound infection in Hinman's[11] (1937) fifty consecutive, pre-antibiotic, plastic closures was twelve per cent.

Fever. An analysis of the postoperative temperature curves of 24 consecutive patients, in sufficiently good condition to require no preliminary drainage, showed the maximum temperature elevation occurring on the second postoperative day, to average 99.9 degrees.

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[8] Lee, L. W., Davis, E. and Barmore, J.: The clinical use of cyclaine (hexylcaine) as an anesthetic agent in urological surgery, A report of observations on 1000 patients. J. Urol., 72: 261–266, 1954.

[9] Young, H. H. and Davis, D. M.: Young's Practice of Urology. Philadelphia: W. B. Saunders Co., 1926.

[10] Watson, F. S.: The operative treatment of the hypertrophied prostate. Ann. Surg., 9: 1–27, 1889.

[11] Hinman, Frank: The modern operation of plastic perineal prostatectomy. Tr. Am. Assoc. Genito-Urin. Surg., 30: 265–279, 1937.

Dismissal on the eighth postoperative day, perineum dry and urinary control satisfactory, is not unusual. Post-prostatectomy hospitalization of the last 50 patients averaged 11.3 days, which figure must be viewed as somewhat exaggerated because a substantial percentage of these patients, after permission for dismissal, voluntarily remained in the hospital one to several days awaiting conveyance, or the arrival of relatives. Of these last 50 patients, seven left the hospital (perineum dry) on the eighth postoperative day, twelve on the ninth, and by the tenth day dismissals totaled 25, or 50 per cent. There were three with 17 postoperative hospital days, and one, the maximum, with 19 days. This conspicuously shortened prostatectomy hospitalization obviously tends to nullify the chief advantage claimed by those favoring the transurethral route.

These figures, however have no real meaning except by comparison with, for instance, Young's[12] average of 32 postoperative hospital days and average fistula closure of 24 days, reported in 1923; also with Hinman's[11] 24 day postoperative average (1937), and our own figure of 21 days, reported as late as 1940. The present-day patient, however, having no basis for comparison, has no realization of the spectacular decrease in hospital days which has been achieved, and the occasional one is disappointed to learn of the 11.3-day postoperative hospitalization average. Thus progress receives no credit.

MORTALITY

Our over-all mortality rate is 2.9 per cent. This includes the entire series of 2050, the good and the poor risks, and all deaths, from whatever related or unrelated cause, dating back over a period of 34 years. The youngest patient was 40 years of age, the average 69 and the oldest, aged 101 at the time of operation, is now 108 It is true that lower mortality rates for perineal prostatectomy have been reported, but not in four-figure series. Until the number of operations becomes conspicuously large Dame Fortune may occasionally play a major role, permitting a factual and rather an imposing report with a zero mortality rate Young[12] in 1923 reported a series of 198 consecutive perineal prostatectomies without a death. His over-all mortality rate, however, reported at this time (1049 operations), was 3 4 per cent, and in 1930 (1571 operations), was 3 6 per cent [13] Similarly our own total series includes three "runs", each exceeding 100 consecutive prostatectomies without a death. Young,[14] in 1939, stated that five consecutive residents at the Brady Urological Institute had performed a total of 217 perineal prostatectomies, with a total mortality of 1.2 per cent. We venture that no one of these residents has maintained this record through the years, unless with small prostatectomy volume. For purposes of comparison

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[12] Young, H H Prostatectomy Preoperative, operative, and postoperative treatment. Surg , Gynec & Obst , **36:** 589-612, 1923

[13] Young, H H The advantages of the perineal route in the treatment of various diseases of the prostate Proc Roy Soc Med , **23:** 65-90, 1930

[14] Young, H H Prostatic obstructions Medical and surgical aspects. New York State J M , **39:** 2241-2252, 1939

TABLE 1. *Reported mortality rates in prostatic surgery*

		Date	Number of Patients	Reported Mortality
	Perineal Prostatectomy			
Hugh Young*	Baltimore	1926	1000	3.2%
Daniel Higbee†	Denver	1951	572	1.7%
Davis and Lee	Omaha	1953	2050	2.9%
	Suprapubic Prostatectomy			
Hunt and Walters‡	Rochester	1938	1000	5.4%
Rees‡	England	1947	242	23.0%
MacDonald‡	Canada	1947	495	39.0%
Galbraith‡	England	1948	318	12.0%
Herman*	Philadelphia	1938	750	4.0%
Freyer*	England	1919	1550	5.3%
Randall§	Philadelphia	1942	340	6.3%
Belleview Hospital	New York	1942		
1 Stage§			208	10.0%
2 Stage§			444	18.0%
Phil. Gen. Hosp.§	Philadelphia	1942	167	34.1%
	Retropubic Prostatectomy			
Millin‡	England	1949	757	4.5%
Jacobs‖	Glasgow	1951	500	6.0%
Newman¶	Sidney, Australia	1951	103	8.0%
Ostenfeld**	Denmark	1951	114	4.3%
	Transurethral Resection			
Nesbit‡	Ann Arbor	1946	2425	1.8%
Univ. Minnesota‡	Minneapolis	1950	1560	1.2%
Mayo Clinic‡	Rochester	1950	11522	1.2%
Lee	Omaha	1954	794	1.7%
Randall§	Philadelphia	1942	315	2.2%
Herman*	Philadelphia	1938	500	2.6%
Kretschmer*	Chicago	1935	551	3.2%
Alcock††	Iowa City	1935	600	4.6%
Cook County Hosp.*	Chicago	1937	283	18.5%
Phil. Gen. Hospital§	Philadelphia	1942	56	18.0%

* Herman: Practice of Urology. Philadelphia: W. B. Saunders Co., 1938, p. 756.
† J. Urol., **69**: 144–151, 1953.
‡ Creevy: J. Urol., **65**: 876–882, 1951.
§ Personal communication.
‖ Lancet, **1**: 1088–90, 1951.
¶ Med. J. Austral., **38**: 574, 1951.
** Acta Chir. Scand., **102**: 447–456, 1951.
†† J.A.M.A., **104**: 734–738, 1935.

table 1 is presented showing mortality figures following the various prostatic surgical procedures reported from various clinics.

The urological surgeon is constantly dealing with major surgical procedures in old age, damaged cardio-vascular-renal systems and prolonged hospitalization.

TABLE 2 *Our own perineal prostatectomy mortality rate, shown gradually increasing through the years, in direct proportion to the number of operations*

Reported	Mar 1927	Nov 1928	Aug 1930	Dec 1931	Apr 1933	Feb 1939	Aug 1940	1953
Journal	A M A	A M A	Colo Med	A M A	Jour Lancet	A M A	A M A	
Number of Operations	107	176	323	378	479	741	831	2050
Mortality Rate	0.93%	1.7%	2.48%	2.38%	2.5%	2.7%	2.7%	2.9%

TABLE 3 *Analysis of causes of 60 deaths among 2050 perineal prostatectomy patients*

Directly related to prostatic surgery		24
Sepsis	15	
Immediate hemorrhage	1	
Delayed hemorrhage	5	
Uremia	3	
Doubtful relationship to prostatic surgery		30
Cerebral "accident"	8	
Coronary thrombosis	6	
Pulmonary embolus	15	
Bronchopneumonia	1	
Wholly unrelated to prostatic surgery		6
Cerebro arteriosclerosis	1	
Femoral embolus	1	
Acute hemorrhagic gastritis	1	
Perforation of colon	1	
Parkinsonism	1	
Intestinal obstruction	1	

As we assume grave risks in increasing numbers, our luck finally plays out and the averages catch up with us. This is as inevitable as sunset. Moreover, actuarially figured, the average mortality rate from "natural", or *all* causes, during the two decades between ages 60 and 80, is 6.3 per cent annually, or 0.5 per cent each month.[15] Therefore, indulging in fancy and estimating an average total hospitalization of one month, one would attain a more nearly accurate index of the actual prostatectomy risk by deducting 0.5 per cent from his over all mortality rate. Superlative surgical judgment and skill must bow to these figures. This inescapable mortality rate is further demonstrated by table 2, compiled from our own published records showing a gradual, fractional increase in mortality rate from 0.93 per cent (107 cases) in 1923, to the present 2.9 per cent, and this in spite of greatly improved methods of anesthesia, hemostasis and technique. We trust that the reader will share our belief that this creeping increase is the result of the inexorable influence of the mortality tables and the averages, rather than evidence of decreasing surgical competence. As remarked by Dr. Richard Chute, we "seem to be flirting with the irreducible minimum." Table 3 analyzes the causes of our 60 deaths.

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[15] Commissioners 1941 Standard Ordinary Mortality Table

COMPLICATIONS

By reason of the inevitable percentage of unfavorable developments, unforeseeable, unpreventable, and often wholly unrelated to the operation, no large series of any major procedure, if meticulously analyzed, may be truthfully reported uniformly uneventful as to convalescence. We have had our full share of troubles and problems. Yet, through the years, it has been possible gradually to eliminate or minimize the various major complications (except vascular "accidents") to the end that our post-prostatectomy convalescence, although not uniformly uneventful, may be described as routinely so. The conspicuous improvement has, in no small measure, resulted from achievements in other than urological fields.

Immediate postoperative hemorrhage is no longer a problem, thanks to clear visualization, suture-ligation and plastic closure, facilitated by the hemostatic traction bag. Our series includes one death due to uncontrollable hemorrhage immediately following operation (No. 3206, October 1927). Upon two occasions only, during the past 9 years, has transurethral aspiration of clots and fulguration of bleeding point been necessary. Postoperative transfusion has been conspicuously rare, and in no instance has transfusion been necessary during the operation.

Massive secondary hemorrhage, occurring suddenly, as late as the end of the second postoperative week, once a grave menace, has yielded to the sulfonamides and the antibiotics. In 1932, one of us[16] reported a 3.5 per cent incidence of this complication, including an "epidemic" of five cases in 13 consecutive operations. Since this amazingly high percentage surpassed the bounds of mere coincidence, the only plausible explanation seemed to be upon a specific infection basis. Before the advent of the resectoscope these five emergencies were successfully managed by transurethral aspiration of clots and endoscopic fulguration. Hinman's[11] report of fifty consecutive pre-antibiotic, plastic closures included four secondary hemorrhages (8 per cent).

This grave and most disconcerting emergency, not having been encountered during the past 6 years, is no longer a cause for concern. This statement, however, does not apply to convalescence following the transurethral operation. In our own experience, the frequency of delayed hemorrhage has been such that we consider it important to keep transurethral patients hospitalized, or at least under observation, for 14 postoperative days. Thus, it has come to be that it is now the perineal prostatectomy patient who may claim the advantage of shorter hospitalization, or at least a shorter period of postoperative observation. We repeat that we cite our own experience only.

Of *vascular "accidents"* (cerebral, coronary and pulmonary) we have had our inevitable share. In addition to many, unrecorded, nonfatal vascular episodes, this intractable triad was responsible for no less than 29 deaths, or 48 per cent of our total mortality (table 3). We also have our thrombophlebitis worries, and perhaps deceive ourselves in thinking that early ambulation has been helpful in reducing the incidence of this *bête noire.* Having no accurate method of balancing usefulness against harmful effects, we are not too happy with the anticoagulants. The injudicious use of this form of therapy was indirectly, but definitely, responsible for one death.

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[16] Davis, E.: Massive secondary post-prostatectomy hemorrhage, controlled by endoscopic fulguration, report of 5 cases. J. Urol., **28:** 365–370, 1932.

Incontinence. Reading Goodfellow's original description of blind, traumatizing, evulsion of the prostate through a median perineal incision carried into the membranous urethra and employing no retractors or other instruments ("the finger serving all needs"), one readily understands why this procedure entered upon its career in disrepute. In fact, the span of half a century has not entirely corrected the misconception that perineal prostatectomy has a monopoly on postoperative incontinence. Those informed, however, recognize that this complication, usually transient, may be noted following prostatic surgery in skilled hands, by whatever route: perineal, suprapubic (retropubic), or transurethral, regardless of flawless technique. The same may occur after internal urethrotomy for urethral stricture. Goldstein and Rubin[17] reported 3 cases of incontinence problems following suprapubic prostatectomy. One of our most troublesome incontinence problems followed suprapubic prostatectomy; another followed internal urethrotomy for urethral stricture. Those who favor the transurethral route acknowledge the same.

A critical consideration by one of us[18] of the possible causes of this troublesome interlude, occurring regardless of surgical finesse, justified the conclusion that weakness or atrophy of disuse of the external sphincter fibers is the major etiological factor rather than mechanical injury of muscle fibers or nerve supply. Upon this theory, sphincter weakness may be said to have been both caused and concealed by the obstructing prostate, and merely revealed by the prostatic surgery. The enlarging prostate had stretched one sphincter (the internal) and relieved the other of duty, thus incapacitating both long before the arrival of the surgeon upon the scene.

With external sphincter and nerve supply intact, following faultless technique by any route, the problem then is merely that of measures directed toward rejuvenation of the muscle fibers by "exercise." The natural or spontaneous process of regaining control may thus be materially hastened by a program consisting essentially of instruction and encouragement, explaining to the patient the importance of making voluntary effort alternately to start and stop the stream during each urination. In the occasional initially completely incontinent cases the bladder is daily filled to capacity through a catheter, and the start stop routine repeated. Close personal supervision is essential. Progress is frequently noted after the first "lesson." The patient did not know he could accomplish this. He had not realized the importance of making the effort. Instruction to tighten the sphincter ani and perineal muscles many times daily, between urinations, gives the patient a consciousness of the perineal musculature which he would not otherwise have. This method of treatment has recently been described by Verges-Flaque.[19] A strychnine, ergot, ephedrine prescription* we believe is helpful in hastening the return of muscle tone.

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[17] Goldstein, A. E. and Rubin, S. W.: Incontinence following suprapubic prostatectomy, with report of 3 cases. Urol. & Cutan. Rev., 50: 664–667, 1946.

[18] Davis, E.: Postoperative urinary incontinance. J. Urol., 65: 93–99, 1951.

Other, less frequent, more troublesome and not generally recognized causes of postoperative incontinence are concurrent neurogenic dysfunction and senile, physical and mental debility. The central nervous system lesion undiagnosed, and/or senility unrecognized as a factor, it is inevitable that the surgeon, who has merely revealed the sphincter weakness by removing the "stopper," should receive full credit for unsatisfactory functional results. We attempt preoperative confirmation of suspected cord lesions by neurologic consultation and cystometrographic study, with a view to forewarning physician, patient and relatives of possible postoperative vesical dysfunction.

Perineal urinary fistula. Whereas seven instances of persistent perineal leakage requiring secondary closure were reported in our first 378 cases, and whereas Young,[12] in 1923 reported an average 24-day duration of perineal fistula, with "14 per cent being open on dismissal," this problem has become insignificant since the advent of the antibiotics and the adoption of routine plastic closure. Secondary closure has not been necessary during the past 8 years.

Acute suppurative epididymitis, of which there were 42 cases included in the report of the first 378 operations, may be eliminated by routine, local infiltration, vasectomy, *if* performed when catheter drainage is initiated. This extremely painful complication may well be more distressing and a more serious matter than the prostatectomy. The importance of vasectomy in connection with prostatic surgery has been pointed out by Goldstein[20] and by Colston.[21]

Postoperative urethral stricture following perineal prostatectomy is a remote possibility, as is the case following any procedure involving urethral trauma, but in our experience has been extremely rare. In this respect perineal enucleation holds a distinct advantage over transurethral resection following which stricture is a recognized hazard, conceded by all. Others have reported post-resection incidence of this complication in percentages varying up to fifteen. By reason of this hazard, perineal urethrotomy, to avoid instrumental trauma to the anterior urethra, has been advocated by eminent authority. Nesbit[22] has advised this method of instrumental by-passing of the anterior urethra, "in any cases where a 30 caliber French steel sound . . . fails literally to drop into the urethra."

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[19] Verges-Flaque, A.: Urinary incontinence following prostatectomy: Its cure by non-operative treatment. J. Urol., **61**: 96–103, 1949.

* Strychnine sulf., 0.195 gm.; fld. ext. ergot, 60 cc; ephedrin sulf., 0.52 gm.; arom. exilir, q. s. 240 cc, given in teaspoonful dosage, 4 times daily.

[20] Goldstein, A. E.: Bilateral ligation of the vas deferens in prostatectomy. J. Urol., **17**: 25–35, 1927.

[21] Colston, J. A. C.: Vas ligation for the prevention of preoperative and postoperative epididymitis. J.A.M.A., **90**: 526–527, 1928.

[22] Nesbit, Reed M.: Transurethral Prostatectomy. Springfield, Ill.: Chas. C. Thomas, 1943, p. 94.

LATE FUNCTIONAL RESULTS

In the quest for the unattainable perfection in any surgical field, the best to be hoped for is a near approach to the ultimate goal, which is the removal of the pathological process and the achievement of symptomatic relief, in high percentage with minimum risk, also with minimum hospitalization Second in importance only to mortality rate and, from some viewpoints and in certain situations, of even greater importance is the recovery of comfort, including restoration of the involved organ to normal function Hinman[11] has said, "Of equal importance with the death rate is the curative rank of a method "

It has come to be generally recognized, by the profession and the laity as well, that prostatic surgery not only may be performed with minimal risk but offers a high percentage of good functional results As the result of improved diagnosis, technique and antisepsis, together with the tendency toward early ambulation and shortened hospitalization, it is perhaps unfortunate that people have come to take too much for granted. They fail to realize that every surgical procedure involving whatever organ has its serious aspects, and that a tragedy, or an operative result short of perfection, might follow even relatively minor procedures, and not infrequently from some wholly unrelated cause

The late functional results of prostatic surgery may be evaluated by follow-up inquiry, including specific questions relating to urination Those who have sought information by the analysis of questionnaire responses from patients in the old age group recognize this as a tedious and rather unsatisfactory process, beset with difficulties and inaccuracies at best Some have died, some have disappeared and others fail to reply, while many, rather than confining themselves to the specific questions, base their dissatisfaction upon wholly unrelated symptoms, such as constipation or "rheumatism " Many are senile and confused mentally, therefore tending to emphasize unrelated complaints We have made two questionnaire attempts, inquiring concerning wound healing, continence, nocturia and ease of urination, including also the vitally important question, "Insofar as the operation is concerned, do you consider yourself well, improved or unimproved?" Since there could be no criterion superseding the patient's own opinion as to his satisfaction with his operative result, this one question alone should suffice, and since this simple and direct method of inquiry should obviously tend to minimize, rather than exaggerate, the number of patients reporting themselves "well," the following summary of results should be viewed as over conservative

The last follow-up inquiry was made in 1940 Of 100 consecutive questionnaire responses reported in a paper by Davis and Nesbit[23] comparing prostatectomy and resection results, 89 patients reported themselves well, 10 improved and one unimproved The opinion of each patient who excluded himself from the "well" classification was accepted as final, without any attempt to sift out those whose complaints and old age disabilities were unrelated to the urinary tract

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[23] Davis, E and Nesbit, R M Comparison of late functional results in perineal prostatectomy and transurethral prostatic resection Am Assn G U Surg , **33** 251–255, 1940

This source of possible inaccuracy, obviously, would tend to reduce, rather than boost, the percentage of good functional results. It is to be noted that these questionnaire responses antedated the antibiotics and our adoption of routine plastic closure.

SUMMARY

From the blind, traumatizing evulsion of a half century ago, perineal prostatectomy has evolved as a procedure of precision.

Notwithstanding the ravages of age and the inexorable law of the averages, an exceedingly low mortality rate may be maintained. Uncontrollable (and in large percentage unrelated), vascular "accidents" are responsible for approximately half of the deaths.

Plastic closure and the newer antibiotics and sulfonamides have contributed largely to the spectacular shortening of postoperative hospitalization.

Of the chief causes for concern ordinarily associated with prostatic surgery, hemorrhage, sepsis, fistula, stricture, incontinence and vascular "accidents", none but the last remains more than a minor problem.

Increasing public prostate-consciousness, resulting in general realization of the hazard and added hospital cost incident to delay, has brought patients in earlier, permitting safe intervention without delay; whereas the time was when the omission of preliminary drainage was viewed in urological circles as nothing short of heresy.

Prostatic surgery need not be dreaded, but rather welcomed as a means of relief. The decision comes to be merely a matter of weighing of alternatives. The patient with residual urine and obstructive symptoms needs but balance the minimum risk and discomfort of surgical intervention against the increasing risk and suffering, and the final inevitable consequence of continued neglect.

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AORTOGRAPHY

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Following the brilliant presentation in 1929 of translumbar arteriography by dos Santos, Lamas and Pereira Caldas,[1] many adverse case reports and papers emphasized the serious nature of the procedure and cited fatalities directly attributable to its use Because of the latter group, a most valuable diagnostic modality had been temporarily sidetracked by many. We were most closely associated with this latter group It was only after the serious efforts of Doctors Nelson[2] and Doss,[3] to whom we owe an apology, that we were induced to give this procedure some serious thought

During our earlier series we used an elaborate apparatus with tubes, special syringes, and attachments, but soon learned that with each additional connection we had another point of possible separation and therefore a failure We reverted to the use of an ordinary needle and syringe, using a No 17 or 18 gauge 8 inch styleted needle and a luer lock 20 cc syringe of normal caliber

The x-ray opaque solution we used is an 80 per cent sodium iodide, as suggested by Ned Schnayerson, who advised the intravenous administration of normal saline to counteract any reaction from this drug

Our technique consists of raising an anesthetic wheel at the junction of the outer border of the lumbar muscles and the lower border of the twelfth rib A 2-inch needle, No 24, is introduced inward medially and toward the body of the vertebrae, depositing 1 per cent novocain as it is advanced This needle is now withdrawn and the 8-inch No 18 needle is introduced and aimed toward the aorta so as to enter it at the level of the lower border of the first lumbar vertebrae After perforating the aorta, blood is noted, aspiration may be necessary to start the flow In high-strung individuals at this time a short pentothal sodium intravenous general anesthetic is induced With the patient anesthetized, a warm solution of sodium iodide is drawn into a warm 20 cc syringe, this facilitates the injection of the dye by eliminating precipitation of the hypertonic iodide, the x-ray technician is alerted and after injecting as rapidly as possible 10 cc of this solution, an exposure is made

Because of the need for speed, co operation, precision, and accuracy, a trained team should perform this procedure

When urokon, neo iopax, or diodrast is used, our patients are given 50 mg of benedryl 20 minutes prior to the injection, to decrease the sensitivity of the patient to these medicaments

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Read at annual meeting, American Urological Association, New York, N Y , May 31, 1954

[1] dos Santos, R , Lamas, A and Pereira Caldas, J L'artériographie des membres de l'aorte et de ses branches abdominales Bull et mem Soc nat de chir , 55: 587–601, 1929

[2] Nelson, A O Arteriography of abdominal organs by aortic injection, a preliminary report Surg Gynec and Obst , 74: 655–662, 1942

[3] Doss, A K , Thomas, N C and Bond, T B Renal arteriography, its clinic value Texas State J Med , 38: 277–280, 1942

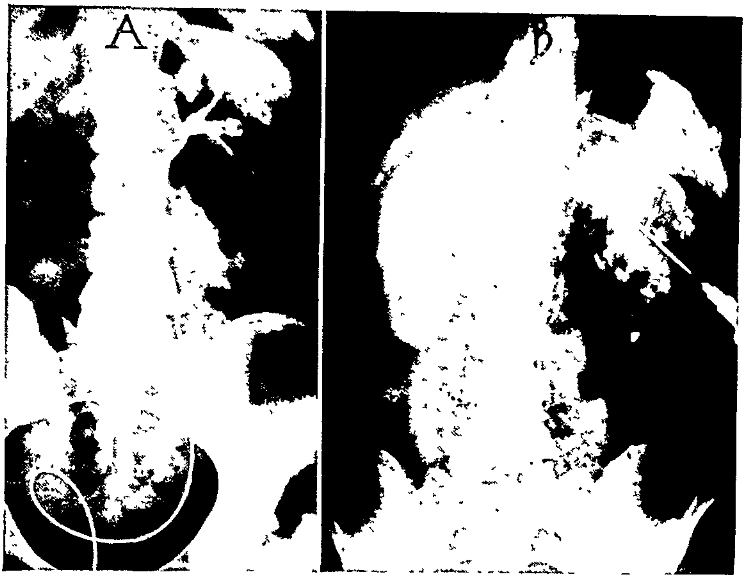

FIG. 1

Aortography should be reserved for diagnosis and not used indiscriminately. Many have carried out arteriography in cases where the pathological process was self-evident. Although we have had no serious complications, the procedure is a formidable one, and an anesthetic is essential. To better evaluate the abnormal, we are compelled to contradict ourselves by stating that normal arteriograms were necessary. No criticism is implied to those who did pioneer investigations on a large series. The contributions of Smith, Rush and Evans[4, 5] have aided us in the differentiation of the normal from the pathological. Since we now have a standard, further study of a large series to establish the normal is superfluous.

INDICATIONS FOR AORTOGRAPHY AND SOME INTERESTING CASES

Group 1. Demonstration of Kidney Tumors

Case No. 8834, Mrs. M., white, was admitted to the New York Polyclinic Hospital in 1953, aged 45 years. She presented a history of hematuria and a report of a previous urological survey with negative findings.

Retrograde pyelogram (fig. 1, *A*) showed a questionable defect in the middle of the left renal cortex. An aortogram (fig. 1, *B*) showed a pooling in the same area. A diagnosis of tumor of the left kidney was made. At operation, a nephroureterectomy was performed and a primary carcinoma of the kidney was found.

Case No. 8702, Mr. M., white, aged 68 years, was admitted to the New York Polyclinic Hospital in 1953. He had been operated on for a tumor of the left kidney, a nephrectomy having been performed and a primary carcinoma found. The patient was referred back to us with a diagnosis of a tumor having developed in the remaining kidney. Our studies were somewhat confusing and an aortogram was therefore suggested.

An aortogram, in which 70 per cent urokon was used, showed the aorta well

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[4] Smith, P. G., Rush, T. W. and Evans, A. T.: An evaluation of translumbar arteriography. J. Urol., **65**: 911–923, 1951.

[5] Evans, A. T.: Translumbar arteriography; a preliminary report. Cincinnati J. Med., **32**: 47–56, 1951.

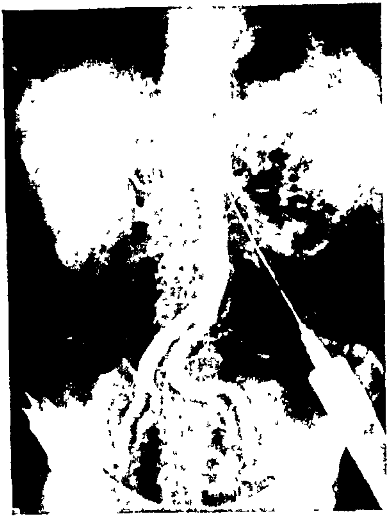

FIG. 2

outlined, the blood vessels of the kidney well defined, and no pooling. To be more certain of our findings, a second film (fig. 2) was taken in the same position using 80 per cent sodium iodide; this showed the vessels much better visualized and again no pooling in the kidney.

The patient died a few months later of intercurrent disease. At autopsy the original exclusion of the kidney tumor was confirmed.

Renal cysts should be placed under the heading of tumors for we still consider them as water or serous tumors. The differential diagnosis often is difficult; nevertheless, when doubt exists, to exclude simple cyst from tumor is important. In the simple cyst, radical surgery is not indicated. We are of the opinion, however, that all cysts demand exploration. In an article in 1930,[6] we reported a case of mesothelial type of hypernephroma involving the wall of what appeared to be a single cyst of the kidney. Total extirpation of the kidney, ureter, and perirenal tissue produced a good result. We followed this case for more than ten years with no evidence of recurrence.

The aortogram (fig. 3) visualized no pooling, and a diagnosis of simple cyst was made. Surgical exposure was advised because of our previous statement and the lesion proved to be a simple cyst.

Group 2. Renal Agenesis

Case No. 1440, Mr. N., white, aged 32 years, was admitted to the New York Polyclinic Hospital March 1952. He complained of dysuria and frequency.

Excretory urography demonstrated an absence of the left kidney and the left

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[6] Ritter, J. S.: Mesothelial type of malignant hypernephroma, within a solitary cyst of the kidney. Am J. Surg, 8: 1089–1091, 1930.

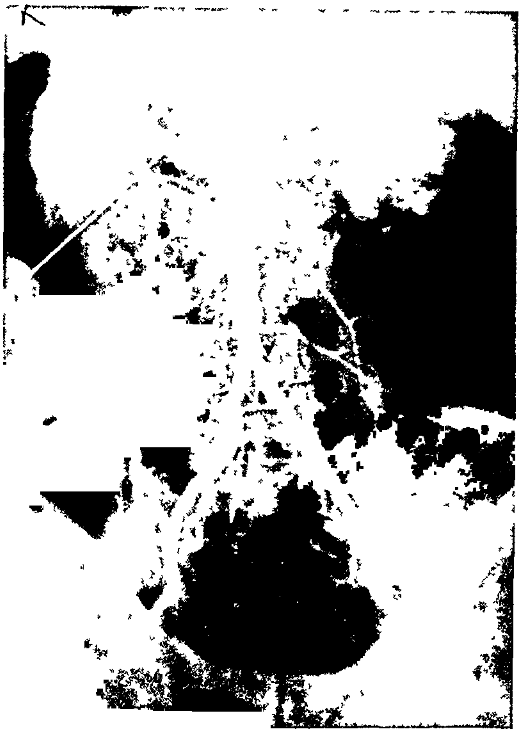

FIG. 3

side of the bladder sharply cut off. At cystoscopy, no ureteral orifice was demonstrable on the left even after injection of indigo carmine intravenously. With these findings one became suspicious of a possible autonephrectomy, left, or a congenital arrest in development.

An aortogram disclosed no renal vessels on the left side, thereby definitely establishing agenesis of the left kidney.

Case No. 1786, Mrs. R., white, aged 32 years, was admitted to the New York Polyclinic Hospital in March 1954, having been referred to the urological department because of a congenital bifid uterus found by the gynecologist. He was interested in determining the presence of associated congenital anomalies.

Cystoscopy was negative except that no right ureteral orifice was demonstrable. Perirenal insufflation, Rivas' technique, in conjunction with an aortogram was accomplished (fig. 4). No oxygen entered the right side of the retroperitoneal space, but did enter the left showing a well-defined kidney with two distinct blood supplies; no renal vessels were seen on the opposite side. Diagnosis: Complete congenital absence of the right kidney.

Group 3. Renal Ptosis

Over many years, nephropexy ran its course of advocates and antagonists. This is no doubt due to the poor selection of patients. Frequently the objection to its use is that no evidences of obstruction are present and therefore nephropexy offers little. The following case refutes this conclusion.

Case No. 6605, Mrs. J. H., white, aged 52 years, was admitted to the New York Polyclinic Hospital October 1952, with repeated attacks of right renal colic, loss of over 20 pounds in weight, and inability to carry on her usual duties.

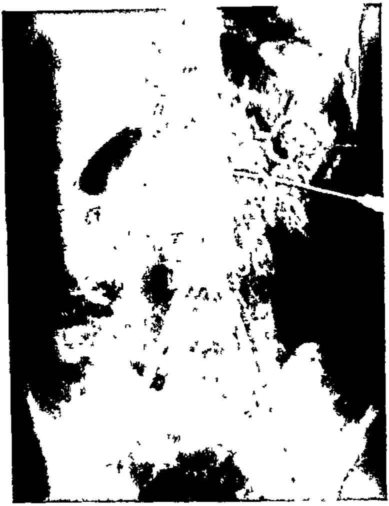

FIG. 4

All findings were negative except a third degree movable right kidney. Nephropexy was frowned upon for there was no demonstrable obstruction to the excretion of urine from the renal pelvis; no persistent kinking of the ureter nor dilation of the renal pelvis were noted.

We advanced the thought of the pain being due to vascular tug. An aortogram was made. The renal arteries show the extent of the deformity. A nephropexy was performed, according to our technique.[7]

The patient has gained 10 pounds and has been free of symptoms. It is now one year and she reports with no complaints. Nephralgia was due to vascular pull and was relieved by surgery.

Group 4. Atrophic Pyelonephritis

It has rarely been our good fortune to follow a patient and obtain a record to demonstrate atrophic pyelonephritis. This patient, seen through the courtesy of Dr. R. B. Hare, Jr., was one in whom a renal calculus had been removed from the right kidney 2 years prior to her visit to New York.

Case No. 7991, Mrs. S., white, aged 32 years, was admitted to the New York Polyclinic Hospital in 1952 because of gradual increasing signs of renal dysfunction and hypertension.

An x-ray demonstrated comparatively normal kidneys functioning within normal range. Two years later a pyelogram of the right kidney, from which a calculus had been removed, showed a contracted kidney, the picture simulating congenital hypoplastic kidney. An aortogram showed a contracted small kidney

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[7] Ritter, J. S and Begner, J. A.: Nephroptosis, a suggested operative procedure for its correction. Urol. & Cutan. Rev., 64: 17-24, 1950.

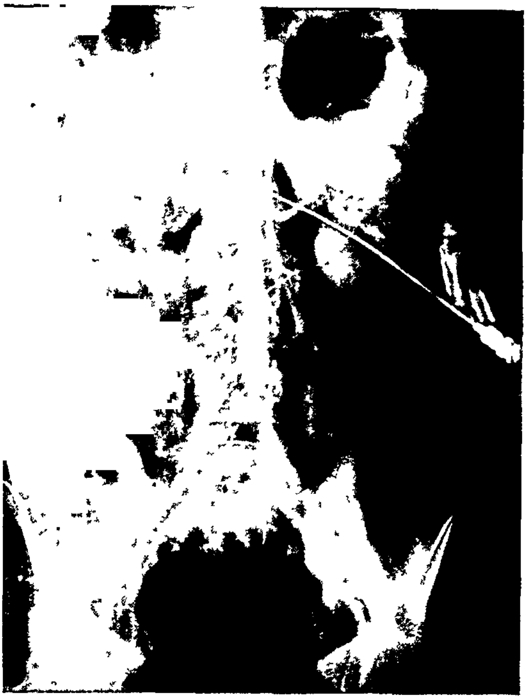

FIG. 5

with a large rigid vessel. Here we have a definite atrophic pyelonephritic organ. A nephrectomy was performed to avoid further production of toxic products.

This patient is much improved and is back at her duties as a mother and housewife.

Group 5. Study of Renal Vascularity

Case No. 4006, Mrs. M., white, aged 45 years, was admitted to the New York Polyclinic Hospital in 1951. She gave a history of hypertension, albuminuria and microscopic hematuria.

A complete urological work-up was essentially negative.

All the usual methods for the control of hypertension complicated by headaches, general malaise, and increasing evidence of diminished vision were of no avail.

Nephro-omentopexy[8] was performed. Two years later the blood pressure had remained at 160 cystolic over 95 diastolic. The patient has been generally improved and is happy.

The aortogram (fig. 5) is the only one of which we know that demonstrates the presence of new vessels in a kidney following nephro-omentopexy.

The purpose of nephro-omentopexy is to increase the blood supply to the kidney. Are we here demonstrating new vessels or are they of omental origin? This can only be answered later. The theory is most entertaining. We are not prepared as yet to make any drastic supporting remarks. In a verbal communication with Ruppert Carter, who was a pioneer in this procedure, we learned that in one case which came to autopsy, new vessels were demonstrated in the kidney subjected to nephro-omentopexy. The fact that our patient is better clinically suggests more work in this direction for the relief of hypertension.

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[8] Ritter, J. S.: Nephro-omentopexy for the relief of hypertension J. Internat. Coll. Surg., 4: 25–28, 1941.

COMPLICATIONS

As previously mentioned, we have had no fatalities due to aortography. Recently, however, we have had a rather interesting, though disturbing complication. A patient was subjected to aortography because of a prolonged history of hypertension. At the time of performing the aortogram, 80 per cent sodium iodide was used. The drug was injected according to the aforementioned technique. The x-ray visualized the hepatic and splenic vessels and their branches. Immediately following the procedure, the patient vomited about one quart of blood mixed with gastric secretions. A second film, taken immediately following the aortogram, demonstrated the gastric mucosal capillaries. A few days following this experience a gastro-intestinal series was done; swollen mucosa of the stomach was found. It is apparent that in this particular case we produced a reaction to the iodide in the gastric mucosa. The patient has progressed favorably with no further gastric disturbances.

In discussing this case, Victor Baum, one of our general surgeons, cited a case performed elsewhere in which the mesenteric vessels were entered directly. This patient died and a mesenteric thrombosis was found at autopsy.

Because of the latter complications, it has been suggested that only 2 cc of dye be injected and a preliminary film be made to determine the site of the injection.

DISCUSSION

We have herewith presented aortograms taken under a simplified technique. We still consider the procedure a formidable one.Its practice has been of inestimable value in the diagnosis of kidney tumors in the demonstration of vascular changes; in presenting congenital anomalous anatomical defects, and in the study of new vascularity to the kidney. In tumor cases, radical nephro-ureterectomy with widespread excision of all adjacent tissue should be carried out. Therefore, the increased information obtained in doubtful cases is a real asset.

This presentation is made to encourage the use of aortography as a valuable aid in the 5 per cent or less urological patients in whom a diagnosis could not be established. The differential diagnosis between cyst and tumor is of utmost importance to the operating urologist. Some added precautions have been suggested.

The 80 per cent sodium iodide solution does give better visualization of the blood vessel than any of the expensive dyes. However, excretory urograms following the aortogram are not obtained. It is our practice to make x-ray exposures 3, 7 and 10 minutes after the aortogram thereby obtaining an excretory urogram. This does not apply when the sodium iodide is used.

It is our wish that this modality be used with discretion and a trained group perform the procedure so as to avoid serious complications that would discredit an excellent addition to our armamentarium.

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URETHROGRAPHY IN THE MALE: THE BOUNDARIES OF THE DIFFERENT URETHRAL PARTS AND DETAIL STUDIES OF THE URETHRAL MUCOUS MEMBRANE AND ITS MOTILITY

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Up to the present time the main purpose of x-ray examination of the male urethra has been to study gross alterations in the contours of the bladder and urethra. In some quarters, for example in Sweden, it has also served as a basis for the study of functional disturbances, by means of micturition examinations.

Urethroscopy for detailed diagnosis of minor pathological changes in the posterior urethra, especially in the region of the seminal colliculus, has been highly regarded by many urologists,[1-4] but it is remarkable that there has been so little interest in the use of urethrocystography for the same purpose. As opposed to the well-known disadvantages of endoscopy as an examination method, urethrography has many advantages. It is easy to perform, safe, and free of discomfort to the patient. The ability of the roentgen examination to compete with endoscopy has, in fact, been demonstrated by pictures of other parts of the body and is, in many respects, very striking.

The method and the contrast medium used, up to now, for urethrocystograms were, however, not ideal for such "detail-diagnosis." For this reason one of us (Morales) devised a new technique based on contrast injection pictures with great distention of the lumen, especially in the posterior urethra, and "emptying" pictures with only a thin layer covering the mucous membrane, thus making possible the reproduction of finer details. For this purpose we have used a new type of contrast medium, highly viscous and water-soluble: umbradil-viscous U (Astra).[5-11]

It is understandable that the same contrast medium cannot be used for examinations of both the bladder and urethra without decreasing the degree of accuracy. The bladder should be examined about half-filled with contrast preparation both at rest and during micturition. The medium for the examination should be so weak in contrast that no details are obscured. A denser medium does not allow more than a detailed study of the silhouette. The urethra, on the

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Accepted for publication May 21, 1954.

[1] Marion, G.: Traité d'urologie. Paris: Masson, 1940.

[2] Millin, T.: Retropubic Urinary Surgery. Edinburgh: Livingstone, 1947.

[3] Praetorius, G.: Zschr. f. Urol., **17:** 129 and 193, 1923.

[4] Winsbury-White, H. P.: Textbook of Genito-Urinary Surgery. Baltimore: Williams & Wilkins, 1948.

[5] Morales, O. and Heiwinkel, H.: Acta radiol. **30:** 257, 1948.

[6] Morales, O.: Acta radiol. **32:** 317, 1949.

[7] Hellström, B. and Holmgren, H.: Acta radiol., **32:** 471, 1949.

[8] Hellström, B.: Acta radiol., **40:** 371, 1953.

[9] Morales, O. and Romanus, R.: Acta radiol., suppl. 95, 1952.

[10] Morales, O. and Romanus, R.: Acta radiol., **39:** 453, 1953.

[11] Morales, O. and Romanus, R.: Nord. Med. **52:** 1179, 1954.

other hand, demands a preparation of relatively dense contrast content to enable observation of possible deformation, dislocations of the lumen, or contrast-filling of fine para-urethral ducts. In this case, however, fine details in the mucous membrane may easily be "drowned." To avoid this, evacuation pictures of the mucous membrane of the anterior and posterior urethra are taken.

The technique is simple: The patient lies on the trochoscope, Knutsson's penis clamp applied. Under fluoroscopic control the contrast medium is injected, thereby distending the anterior urethra until the pressure there overcomes the resistance from the external sphincter. The contrast material then passes through the posterior urethra up into the bladder and runs along the bladder floor down to its lowest point, forming the so-called "vesical contrast band," which should not be interpreted as lying in an elongated posterior urethra.[12] Here, it gradually mingles with any urine that may be present. If the patient contracts the pelvic floor immediately the injection is discontinued ("cuts off as if to interrupt urination," or "hold back flatus"), the contrast material in the diaphragmatic part of the posterior urethra is seen to empty due to contraction of the external sphincter. At the same time, or immediately afterwards, the rest of the posterior urethra contracts and a certain amount of contrast material empties up into the bladder. With the contraction of the pelvic floor musculature (the levatores ani) the prostate and the adnexal organs are lifted upwards some centimeters and slightly forward. The upward movement is most pronounced at the urethral orifice, and the forward movement most at the prostatic apex. If, on the other hand, the patient "strains down" a corresponding downward movement of the pelvic organs is observed, the internal orifice being pressed down while the prostatic apex is simultaneously displaced slightly forwards. During micturition this downward movement is even more pronounced than when "straining down," so that the prostate often seems to be thrown backwards and downwards.

By observing this motility in the lower urinary tract one can get some idea of the occurrence of fixation in, for instance, unilateral or bilateral perivesiculitis with adhesions to the walls of the pelvis, or in infiltration of a prostatic cancer. Here, of course, the motility will be curtailed or stopped on the side of the fixation. The majority of patients examined urethrographically complain of micturition difficulty. It is, therefore, understandable that most patients with hypertrophy or cancer of the prostate are unable to co-operate to give a legible micturition picture. This motility examination, however, is easy to perform correctly, and in general enables better evaluation of the motility of the lower urinary tract than the micturition examination. The micturition picture should, however, always be attempted, as it gives a more complete picture of the micturition conditions, especially the degree of active dilatation in the bladder neck, often accounting for the patient's trouble.

The evacuation of the posterior urethra gives a picture which enables exact determination of the boundary between the prostatic and diaphragmatic parts of the urethra, as the external sphincter normally empties the diaphragmatic part of the urethra completely. The lowest point to which the streaks of contrast

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[12] Knutsson, F.: Acta radiol., suppl. 28, 1935.

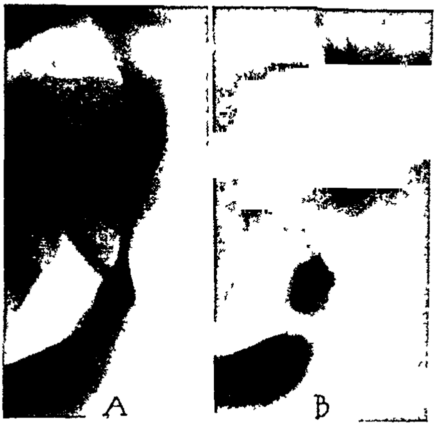

FIG. 1. Boundaries between different parts of urethra. Effect of contraction of musculus compressor nudae. This picture of proximal part of anterior and whole posterior urethra is normal except for moderate widening of prostatic urethra, especially prostatic sulci, indicating slight chronic prostatitis (prostatic atrophy).

In contraction picture (*B*) anterior urethra ends upwards in pointed cone, marking boundary between anterior and posterior urethra. Evacuated section above this corresponds to diaphragmatic urethra, upper border of which lies where rest of contrast material ends downwards in prostatic urethra. (In injection picture (*A*) this point is marked by fine indentations corresponding to endings of distended prostatic sulci.) (Note elongation of diaphragmatic urethra, due to contraction of external sphincter.) Internal orifice of urethra is marked by fine indentations, above which broadening contrast material represents "vesical contrast band" inside bladder. In (*B*) incurvation of lumen of anterior urethra below cone of contrast medium is due to contracted musculus compressor nudae, and material lying above this marks pars nuda. (Compare with fig. 5.)

medium reach in the prostatic urethra then marks the boundary. In the injection pictures, however, the prostatic sulci also appear, as a result of the marked distention of the posterior urethra by the contrast medium. The distal limit of these sulci corresponds to the boundary between the prostate and the urogenital diaphragm. In cases of a pathologically widened prostatic urethra (so-called prostatic atrophy) this can be seen clearly, but in normal cases the sign is more subtle (fig. 1).

The boundary between the anterior and the posterior urethra, the lower boundary of the diaphragmatic part, clinically more important, is marked in contraction pictures by the point of the cone of contrast medium in the anterior urethra. A little way down this cone an incurvation of the anterior wall of the urethra is quite often seen to appear (figs. 1 and 5). It is caused by a tendinous plate belonging to a fine muscle covering the most dorsal portion of the cavernous tissue, between this and the bulbo-spongiosus muscle. It varies in size and position, and was first described by Kobelt.[13] We have studied it in detail roentgenologically and called it the *musculus compressor nudae*.[10] The name refers to the pars nuda, the highest portion of the anterior urethra, which is not covered by musculature or cavernous tissue: it is "naked". It is formed where the urethra, after passing through the urogenital diaphragm, bores obliquely down forwards into the cavernous tissue. The tendinous plate of the musculus compressor nudae lies immediately against the anterior, and in part against the lateral, wall

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[13] Kobelt, G. L.: Die mannlichen und weiblichen Wollustorgane des Menschen. A. Emmerling Verl., Freiburg, 1844.

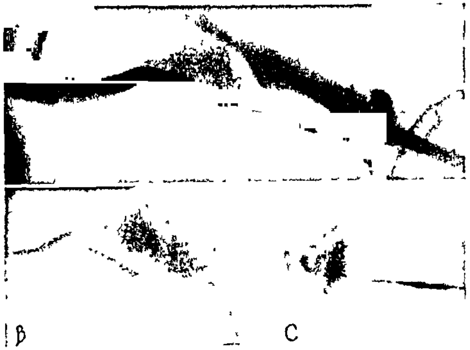

FIG. 2. Post-dilatation pictures from patient with strictures. Injection picture (*A*) shows well distended, though slightly irregular, urethra; emptying pictures (*B* and *C*) reveal rigid, incompletely collapsed walls at stricture sites.

of the urethra, delimiting the pars nuda from the rest of the anterior urethra: pars cavernosa. This incurvation has been observed roentgenologically and described earlier as being a stricture or contraction of the external sphincter (in which case the boundary between the anterior and posterior urethra has been incorrectly drawn).

The rest of the anterior urethra appears in the injection pictures as a uniform tube without any details except in the silhouette. If the urethra empties as a result of the elasticity of the mucous membrane and adjacent tissues, a slight amount of contrast medium remains on the mucous membrane, seen as a hair-fine, even streak. The appearance and elasticity of the mucous membrane may then be studied. In cases of decreased elasticity, for instance in the earliest phase of the development of strictures, the mucous membrane can no longer close up in the same gentle manner, thus leaving parts of the lumen open (fig. 2).

A further advantage of the motility examination is that contrast filled para-urethral ducts and cavities are more readily demonstrated. Normally these are not filled with contrast material. From a diagnostic standpoint it is, therefore, necessary to fill a duct only a few millimeters for it to be clearly visible in the roentgen picture. The use of a contrast medium of greater density facilitates diagnosis; further, the use of the voluntary pelvic floor contraction procedure contributes to the clarification by showing that the medium in the para-urethral structures changes position in relation to the bony structures of the pelvis but not in relation to the urethra. Higher viscosity actually results in a decrease in the rate of flow in the capillaries, in comparison with low viscosity media, but this is of no great importance in practice (see below).

A complete urethrographic examination of the male urethra should, therefore, include: pictures exposed a) during injection with the lumen fully distended, b) during contraction of the pelvic floor, and c) during micturition. The first pictures (a and b) should always be taken with fluoroscopic control in at least three different projections: a frontal and two oblique pictures from both sides

(30–40 degrees rotation). A ninety degree lateral view may also be of value, and is made possible by the high contrast content of the medium. The micturition picture should be taken in one of the oblique positions, making comparison between the injection, the contraction, and the micturition pictures possible.

This technique demands certain *physical properties* in the contrast medium in addition to those of the usual urography contrast media. To produce distention, that is to exert sufficient pressure in the posterior urethra, it must be highly viscous, and at the same time it must be soluble in water and possess wetting qualities. It should, then, be able to moisten mucous membrane and mingle with the body fluids (as opposed to, for instance, iodized oils). These properties are not incompatible as has so often been supposed. High viscosity can be combined with water-solubility and wetting qualities, so enabling the medium to penetrate capillaries (para-urethral ducts).

Viscosity is a property common to all fluids and depends on internal friction between the molecules. A highly viscous substance is "thick", and one of low viscosity "thin". High viscosity is associated with increased frictional resistance. The rates of flow of various fluids in laminar flow and under otherwise similar conditions, are inversely proportional to their viscosities.

Kinematic viscosity is measured in stokes. The following approximate viscosity values in centistokes (cSt.) (one one-hundredth of a stoke) are given for comparison: water = 1; umbradil (35 per cent solution) = 1.5; jodipin 40 per cent neu = 200; umbradil-viscous H = 300; umbradil-viscous B = 700; castor oil = 1100; glycerol = 1450. The viscosity of umbradil-viscous U at 37° C. is 2000 cSt.

The resistance during injection of the preparation is considerable, due to internal friction. In order to obtain a satisfactory flow the injection pressure must be much greater than when injecting low viscosity solutions, but can be made with ease by hand with an ordinary syringe. This high initial pressure is almost entirely expended in overcoming friction. In other words, the injection force is in the main translated into static pressure, and only a small part of it is changed into kinetic energy (fluid velocity). The highly viscous solution has a very low velocity as it flows into the bladder, and the lumen of the posterior urethra is satisfactorily expanded. This means that there is a rather high right-angle pressure against the walls. To obtain a pressure and a distention of the posterior urethra corresponding to that produced by a high viscosity solution, a low viscosity medium would have to be injected at a quite unreasonably high rate. By such a sudden injection at high pressure at the moment of exposure it is possible, however, to obtain a fairly good dilatation of the posterior urethra even when a low viscosity solution is used, but the method has its disadvantages. The patient may easily tense the pelvic floor and with it the external sphincter, the danger of mucous membrane damage and of urethro-cavernous reflux is increased, et cetera. On the other hand, when a high viscosity contrast fluid is used the procedure is calmer, the variations in the injection pressure are less noticeable, and flow is equalized by the resistance of the fluid. It is, therefore, easier to maintain an even, high pressure. It would appear that the dangers of

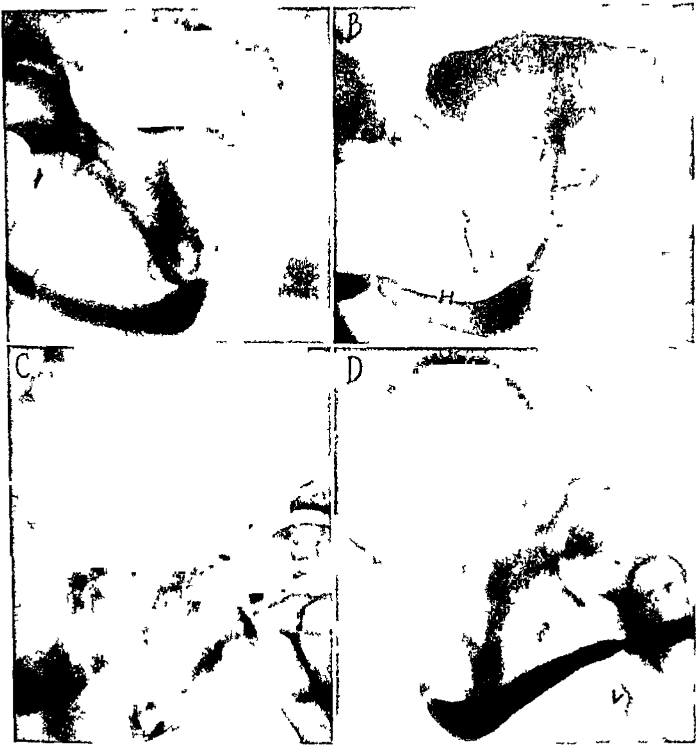

Fig 3 Urogenital infection for 25 years Transurethral resection was performed for sclerosis of bladder neck Clinical and roentgenological findings were in agreement strictures, displacement of diaphragmatic urethra due to enlargement of left bulbo urethral (Cowper's) gland (just below inferior arrow), contrast filling of prostatic utricle, postoperative irregularities in supracollicular portion of prostatic urethra, trabeculation of the bladder (*A*) and (*C*) made with low viscosity preparation, (*B*) and (*D*) with highly viscous medium, technique being same (*A* and *B* injection, *C* and *D* micturition pictures) (In this, as in most subsequent figures, arrows point in descending order to internal orifice, upper and lower ends of verumontanum, and apex of prostate)

mucous membrane damage and of urethro-cavernous reflux are less, despite the higher pressure, than when a low viscosity solution is used at a definitely lower pressure

The occurrence of reflux appears to be less frequent the higher the viscosity of the contrast medium [9] This can probably be explained by the fact that the quick variations in the extension of the mucous membrane decrease the higher the viscosity (although the distention, as such, increases) the local damage to the mucous membrane being caused by the *variations* in pressure, and consequently distention, when injecting low viscosity preparations

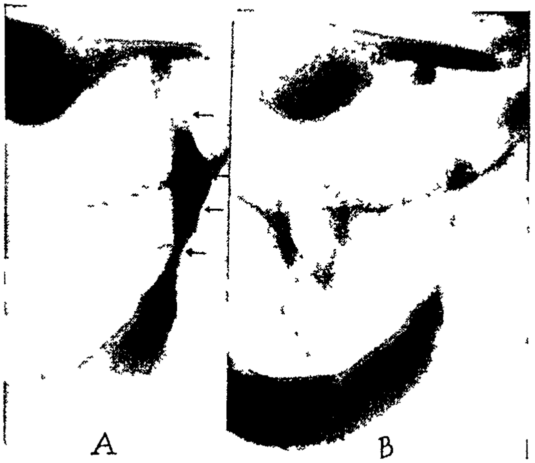

FIG. 4. Hematuria. Normal picture with low viscosity urethrocystography. With high viscosity method, polyp-like defect was seen immediately below flattened seminal colliculus; and practically entire prostatic urethra was nodular. Urethroscopy verified granular polypoid urethritis. (*A*, injection; *B*, contraction picture.)

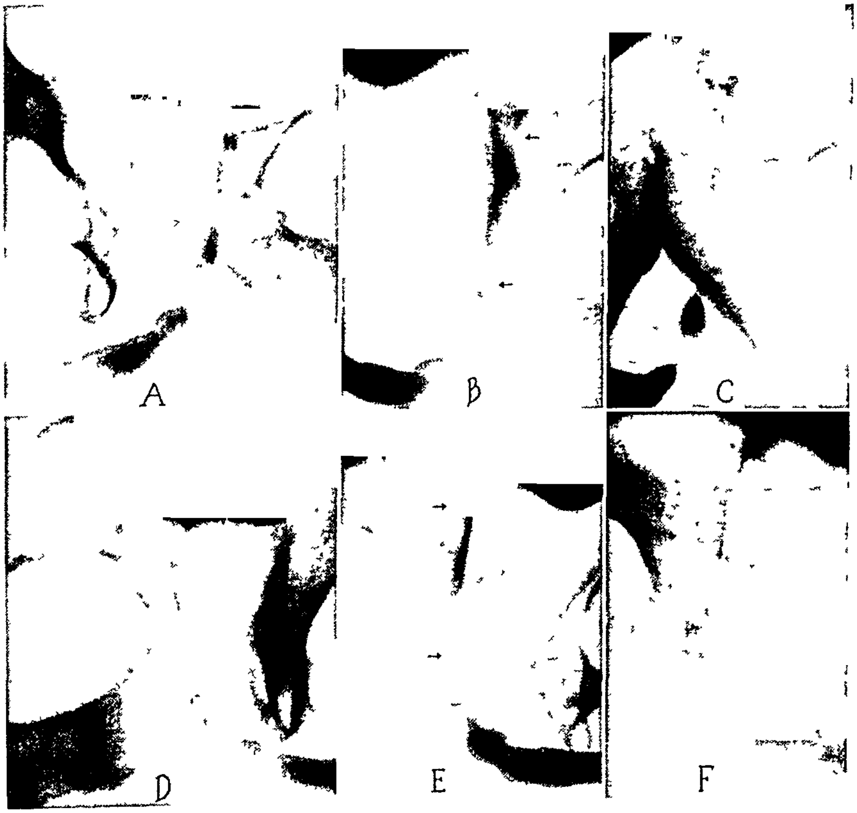

FIG 5. Cancer of prostate treated with hormones and endo-urethral resection. Low viscosity examination (*A* and *D*) revealed nothing of significance except strictures in anterior urethra; in contraction pictures with umbradil-viscous U (*C* and *F*) mural irregularities in prostatic urethra and bladder floor indicate progression of carcinoma, although bladder neck is still wide open, as shown by injection pictures (*B* and *E*), which did not indicate new operation. Micturition picture not obtainable. Musculus compressor nudae is seen to be present in contraction pictures (*C* and *F*). (Compare with fig. 1.)

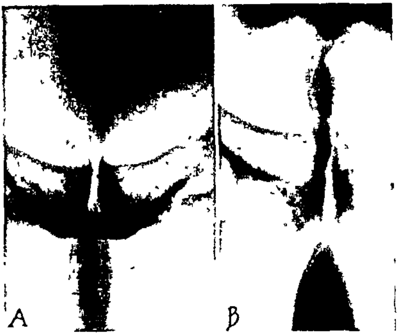

FIG. 6. Low viscosity examination (*A*) failed to reveal cause of patient's urinary difficulties. With umbradil-viscous U (*B*) small adenoma is seen in upper portion of supracollicular urethra.

The advantages of using a highly viscous contrast medium do not, however, lie solely in its ability to produce more complete distention of the posterior urethra. For such a purpose a viscosity of 200 to 500 cSt., as in iodized oils, umbradil-viscous II, or visco-rayopake, is sufficient. These distention pictures with massive contrast filling should, as aforementioned, be supplemented by emptying pictures. When the injection of a low viscosity solution is interrupted, the posterior urethra normally evacuates into the bladder spontaneously, immediately, and completely. When the high viscosity medium is used, however, this emptying occurs slowly—the emptying time is prolonged. The most satisfactory viscosity lies in the neighborhood of 2,000 cSt. at a temperature of 37°C., or approximately that of thick molasses. This viscosity provides good distention of the entire urethra and the evacuation of the posterior urethra takes place at a rate so slow that it may be studied with fluoroscopy without difficulty. As a result of the wetting qualities of the medium and its high viscosity it adheres to the mucous membrane; after compression by voluntary contraction of the pelvic floor, a layer will remain which is sufficiently thin for detailed studies of the mucous membrane relief.

From the viewpoint of physics it should be pointed out that high viscosity in a contrast medium lessens its rate of flow, but does not prevent it from penetrating fine ducts or capillaries. The decisive factor is the preparation's capacity of mingling with the secretions already in the ducts. "A low surface tension and high adhesion to the walls of the capillary will be required for a good penetration, and the viscosity is the resistance to motion."[14]

The decrease in the rate of flow in the capillaries is, however, of no importance in urethrography performed with umbradil-viscous U. This is to a great extent due to the appreciably higher pressure at the orifices of the para-urethral ducts, providing better conditions for the penetration of the contrast medium in comparison with low viscosity preparations.

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[14] Adam, N. K.: The Physics and Chemistry of Surfaces. Oxford Oxford Univ. Press, 1942, 3rd ed.

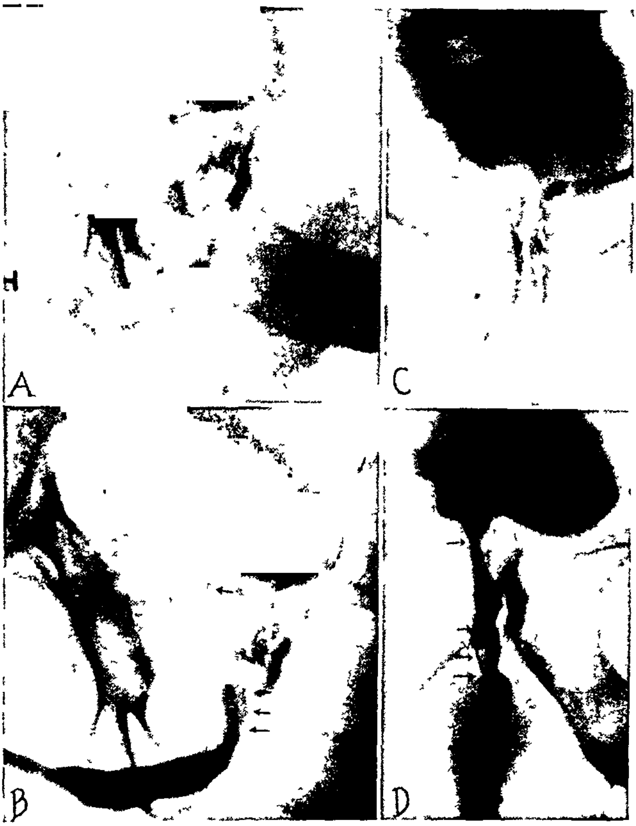

FIG. 7. Cancer of bladder treated by surgery and radiotherapy. Cystoscopy impossible due to scarring. Low viscosity method (*A* and *C*) showed conglomeration of cavities within prostate. With high viscosity material (*B* and *D*) topography became clear and most of cavities could be identified as seminal vesicle and ampulla of vas deferens, as well as a few centimeters of vas itself (upper arrow in *B*). Contrast filled lacunae in anterior urethra were an incidental finding.

In *Acta Radiologica* (Suppl. 95, 1952) we have reported the results of examinations of a series consisting of 85 cases in which the two methods were used concurrently. The new method and the new contrast medium have considerable diagnostic advantages over the low viscosity method.

We give illustrations of some typical cases from this series (figs. 3 to 7) showing the differences in the methods and some of the advantages of the new method.

CONCLUSIONS

A complete urethrographic examination of the male urethra should preferably include pictures with the lumen fully distended (in order to demonstrate strictures, deformities, and displacements of the lumen), compression or evacuation pictures (to establish the boundaries between the different urethral parts, to show finer alterations in the mucous membrane and possible fixations in the pelvic urogenital organs) and, if possible, micturition pictures (for studying normal and pathological micturition).

The urethrographic examination should include the vesical trigone and posterior portion of the bladder floor, since pathological conditions in the male accessory sexual glands are often associated with changes here. The rest of the bladder, on the other hand, belongs diagnostically and pathologically more with the upper urinary passages and is more suitably examined in the course of urography.

Any type of contrast preparation produces satisfactory distention of the anterior urethra in retrograde injection. To obtain adequate distention of the posterior urethra, however, a highly viscous preparation of great contrast density is required.

A water-soluble, highly viscous preparation which adheres to the mucous membrane is necessary to show the mucosa in relief by means of evacuation pictures.

The anterior urethra empties passively, while evacuation of the posterior urethra is best accomplished by active contraction of the pelvic floor. Movements of the bladder floor, prostatic urethra, and adnexal glands may also be studied at the same time.

If the contrast agent has a high contrast density it also contributes to the demonstration of contrast filling of para-urethral passages. In addition, the material should be able to "wet" the mucous membrane and be miscible with the secretions in the passages. High viscosity does not prevent this. The pelvic floor contraction technique also facilitates the identification of contrast material located in para-urethral structures around the posterior urethra.

Mucous membrane anesthesia should always be used for the patients' comfort and to reduce possible reflex muscle contraction.

Fluoroscopic control facilitates the examination and reduces the danger of urethrocavernous reflux.

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SPERMATOCYSTOGRAPHY IN PATIENTS WITH SPINAL CORD INJURIES

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The literature is replete with reports of urinary and genital disturbances in patients with spinal cord injuries. Yet, no reference could be found which dealt with spermatocystography in such cases. The objective of this investigation was to determine whether radiographic changes occur in the spermatic vesicles, how much infection, as manifested by white blood cells, is present in seminal washings, how many—if any—spermia can be counted in the irrigated fluid; whether motile sperm can be seen which may encourage artificial insemination and finally whether the findings of seminal washings parallel those of testicular biopsy. Fifty patients with spinal cord injuries underwent spermatocystography and on twenty-five of these an additional testicular biopsy was done. The following paragraphs report our experience.

MATERIAL AND METHODS

The distribution of level and extent of lesion which was traumatic in all cases were as follows: Cervical, complete: 1 case; cervical, incomplete: 9 cases; thoracic, complete (1–6): 10 cases; thoracic, complete (7–12): 18 cases; thoracic, incomplete (7–12): 7 cases; lumbar, complete: 2 cases; lumbar, incomplete: 3 cases. The age ranged from a minimum of 19 years to a maximum of 58 years; 24 patients belonged to the age group between 20 and 29 years, 16 patients to the group between 30 and 39 years, 7 patients to the group between 40 and 49 years, 2 patients were 50 and 58 years old respectively and one patient was nineteen. The shortest time interval between injury and spermatocystography was 4 months and the longest 110 months. In detail the distribution was as follows: Interval: 1–12 months: 10 cases, 13–24 months: 5 cases, 25–48 months: 11 cases, 49–60 months: 6 cases and 61–120 months: 18 cases.

A 35 per cent solution of diodrast was used as contrast medium. The patient was placed on a Kelley-Koett cystoscopy table in lithotomy position; the genitalia were aseptically prepared and draped. Novocain, 1 per cent solution, was subcutaneously injected locally when this was necessary. The vas was fixed between index finger and thumb and exposed from an incision of 2–3 cm. in length. It then was isolated for a distance of approximately 2½ to 3 cm. in order to permit a Penrose drain to be passed around it and was lifted from its bed with mild traction. This was done bilaterally. The bladder was irrigated with a 5 per cent glucose saline solution until the returning fluid became grossly clear and the catheter remained in the bladder. A flat film was then taken. Thereafter the index finger was introduced below the vas and it was straightened

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by gentle traction. A No. 23 gauge needle, attached to a 5 cc syringe containing 5 per cent glucose in saline was introduced into the supported portion of the vas. Irrigation was performed by exerting maximal pressure on the plunger. The injected fluid was aspirated from the bladder by an assistant. Thereafter 15–20 cc of a 35 per cent solution of diodrast was instilled into each vas through the same needle and finally the bladder was irrigated with 5 per cent glucose in saline in order to wash out all dye. The catheter was removed and x-ray pictures were taken. This procedure was done individually on each side. The needles were left in place in order to repeat the injection, when necessary. The pictures were reviewed, and—provided that they were satisfactory—the wound was closed by 2 to 3 catgut sutures of the skin.

With the exception of 2 cases seminal washings were examined in all patients: *first a wet mount slide was made in order to estimate the number of spermia per high power field, their motility, the presence of bacteria, white and red blood cells. Then the entire specimen was centrifuged for 10 minutes at 200 r.p.m. The supernatant portion was measured and discarded. If the initial wet mount had not shown sperm, the sediment was examined. When spermia were present the sediment was added to a volume of saline and the number of spermia was determined by means of the standard red blood counting chamber. In order not to exceed 150 spermia per 5 squares and to obtain an equal distribution the amount of added diluting saline was kept proportional to the number of spermia found in the high power field of the wet mount; e.g. if only up to 5 spermia were found 2 cc of fluid were added whereas if 50 or more spermia were seen 10 cc were used. The number of spermia was calculated for the entire volume of the seminal washings.

Twenty-five patients underwent a testicular biopsy which was graded† according to the scale of Bors, Engle, Rosenquist and Holliger[1] from grade 1 (Sertoli cells only) to grade 7 (normal cell population). An additional lipid and cholesterol study was done‡ which will be reported elsewhere.

OBSERVATIONS

Spermatocystography was attempted bilaterally in all cases but due to pathological changes of the vas, epididymectomy or orchiectomy, it could be done only unilaterally in 6 patients and was not possible at all in one whose vasa were obstructed and filled with caseous nonspecific material. No complications were observed following spermatocystography including the case with extravasation (fig. 3, *A*). In 2 patients the examination was repeated after 7 months without difficulty. None of the patients experienced pain on washing or filling the seminal vesicles under pressure.

The interpretation of the roentgenograms followed the classification of Pe-

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* The laboratory examinations were performed by Mr. R

† The histological evaluation and grading were done by D
gical Pathology Section, Laboratory Service, V. A. Hospit

[1] Bors, E., Engle, E. T., Rosenquist, R. C. and Holliger,
males, a preliminary report on endocrine studies. J. Clin. E

‡ The histochemical studies were done by Dr. D. C. Barraclough, Department of Anatomy, Medical School, University of California at Los Angeles.

TABLE 1. *Distribution of spermatocystographic findings according to level and extent of injury*

	Number of Spermatic Vesicles				Number of Cases
	Normal	Ectasia	Hypoplasia	Atrophy	
Cervical: C	1	1	0	0	1
Cervical: I	5	3	8	0	9
Thoracic: 1–6 C	3	1	7	6	10
Thoracic: 7–12 C	11	14	5	7	19
Thoracic: 7–12 I	1	7	0	2	6
Lumbar: C	2	0	2	0	2
Lumbar: I	2	4	0	0	3

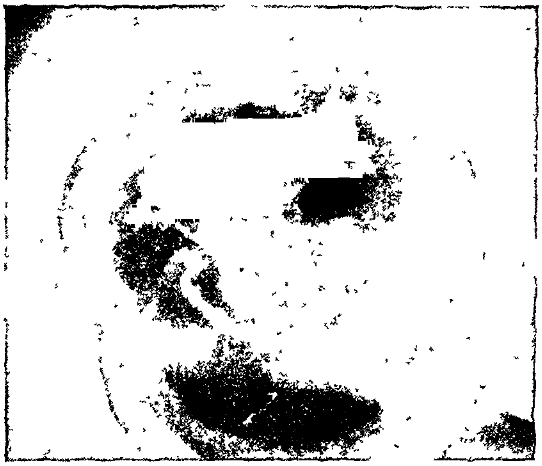

FIG. 1. Normal spermatocystogram. D. M., 22 years; 9 months after injury, L-4, complete.

reira,[2] accordingly the observations were determined as normal, ectasia, hypoplasia and secondary atrophy. Reflux from one ejaculatory duct to the other was seen in 2 patients, filling of the prostatic cavity in 1 case and ectasia of the ampulla of the vas in 5 patients. A cyst of one spermatic vesicle was encountered once. The observations are illustrated in figures 1–3.

The distribution of the spermatocystographic findings according to the level and extent of injury is presented in table 1. There seems to be no correlation although hypoplasia occurred more often in patients with incomplete cervical and high thoracic lesions while, normal, ectatic and atrophic vesicles were numerically highest in patients with complete thoracic lesions between T-7 and T-12. Almost two-fifths of all patients belonged to this group and no significance can therefore be ascribed to this fact.

On evaluating the age of the patient and the duration of the lesion respectively in regard to the spermatocystogram the following was found: Normal spermatocystograms were seen even 9 years after injury and in patients more than 50 years old. No correlation could be established between age of patient, duration of the lesion, and spermatocystographic findings.

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[2] Pereira, Athayde: Roentgen interpretation of vesiculograms. Am. J. Roentgenol. Rad. Therapy & Nuclear Med., **69**: 361–379, 1953.

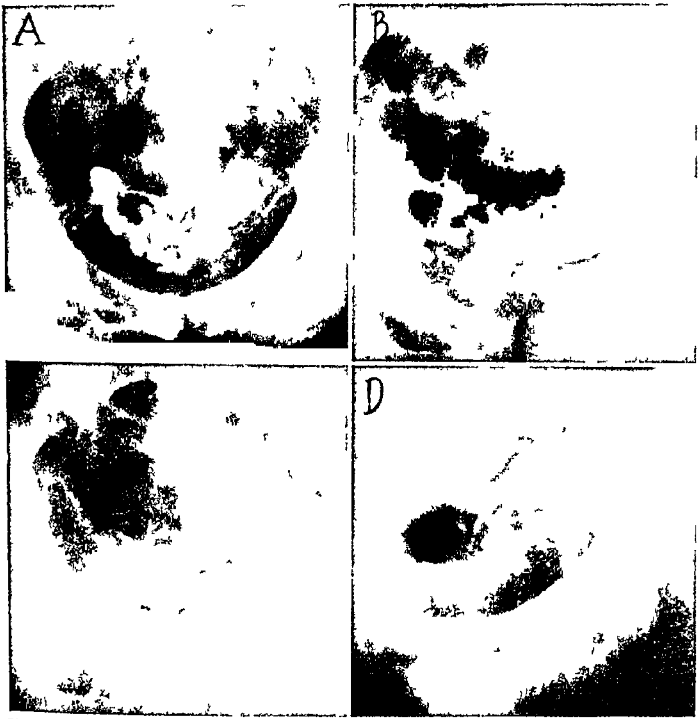

FIG 2 *A*, ectasia D C, 29 years, 105 months after injury, L 2, incomplete *B*, cyst of ght, ectasia of left and right ampullae of vas R W, 12, complete *C*, filling of prostatic ducts, ectasia 40 months after injury, T-4, complete *D*, reflux of contrast medium from left vas into right ejaculatory duct which could not be filled from right vas because it was atrophic and its lumen was obliterated Note ectasia of left ampulla of vas and of proximal part of seminal vesicle while its distal part is atrophied E K, 26 years, 77 months after injury, T 10, complete

No correlation was found between the appearance of the spermatocystogram and testicular biopsy respectively, i e a normal vesiculogram may be connected with a low grade testicular biopsy or vice versa secondary atrophy of the seminal vesicles may be associated with a good testicular condition

Seminal washings were examined in all but 2 cases, however, in 22 cases no spermia were found in the irrigated fluid, yet, in one of these cases a testicular biopsy of grade 6 was present Surprising also was the scarcity of leukocytes which could be demonstrated in only 2 cases with a maximum of 15/hpf The sperm count varied greatly and ranged from zero to 2,300,000 maximum Motility was encountered in only 19 washings of 12 patients, the maximum of motile spermia was 50 per cent, the accompanying count was 6,800 There was

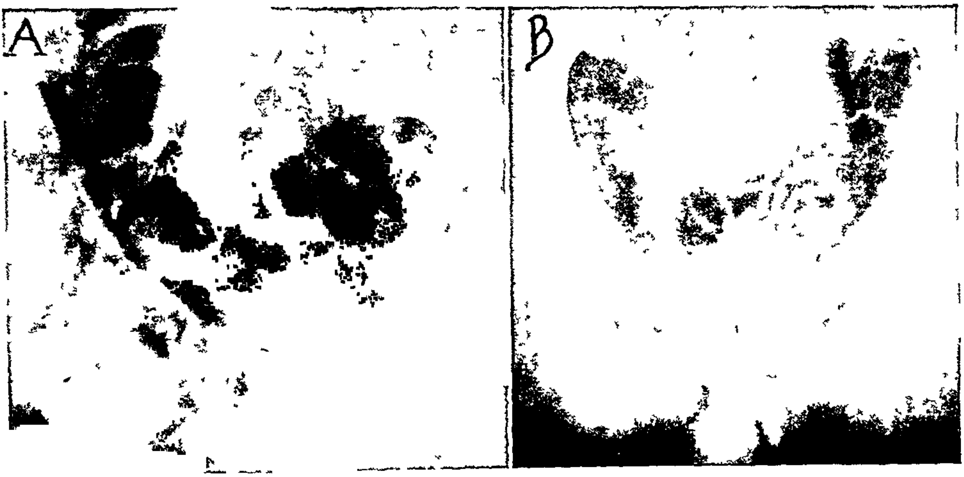

FIG. 3. *A*, extravasation of dye along Denonvilliers' fascia from left spermatocystogram, mild hypoplasia of right spermatic vesicle. J. L., 41 years, 76 months after T-10, complete. *B*, normal left spermatocystogram Atrophic right seminal vesicle and atrophic ampulla of vas. P. K., 26 years; 70 months after injury, T-6, complete.

no correlation between sperm count, motility, quality of testicular biopsy and level or extent of injury.

DISCUSSION

The historical development of spermatocystography has been explicitly reported in recent articles.[2, 3] Description of technical details are included in these publications and were also discussed by those authors who performed epididymography and vesiculography.[4, 5] A special clamp was found unnecessary, which some operators used for the percutaneous fixation of the vas. The nonirritant and re-absorbable diodrast was selected as a contrast medium and was injected in amounts which were up to ten times greater than those reported in the literature. This was necessary because none of our patients complained about pain when the vesicles were full as described by Pereira[2] for patients without nervous damage.

Pain from distention was absent even in those patients whose sympathetic nerve supply was considered to be intact (low lumbar and/or cauda equina lesions). The importance of this observation is obvious because it implies that afferent pathways from the spermatic vesicles do not course with sympathetic nerves; it complements the findings of Retief[6] who following sympathectomies failed to see motor disturbances of emission, and who conceded sympathetic motor innervation only for the smooth muscle of the vesical neck because he observed regurgitation of sperm into the bladder. He went so far as to postulate that the male adnexa received a parasympathetic motor nerve supply rather

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[3] Tucker, A. S., Yanahigara, Hanabusa and Pryde, A. W.: A method of roentgenography of the male genital tract. Am. J. Roentgenol., Rad. Therapy & Nuclear Med, 71: 490-500, 1954.

[4] Boreau, J., Elbim, A., Hermann, P., Vasselle, B. and Flua, [illegible] idymographie. La Presse méd., 59: 1406–1407, 1951.

[5] Boreau, J., Vasselle, B [illegible] agailloux, S : Étude radiolog [illegible] oies génitales normales et pathologiques [illegible] La Presse méd, 61: 1–4

[6] Retief, P. J. M : Phy [illegible] turition and ejaculati [illegible] can Med J., 24: 509-512, 1950.

than a sympathetic. The presented evidence of absent pain on distention with presumably intact sympathetics suggests that afferent fibers travel with parasympathetic nerves to sacral segments. This is corroborated by clinical experience with referred pain from the prostate which may project to both, the lower lumbar and the perineal region. The report by Retief[6] and our own observations make further studies on the innervation of the spermatic vesicles desirable.

Reports by Rose[7] are contrary to the observations of Retief;[6] he observed that a sympathetic anesthetic block is followed by enlargement of the spermatic vesicles. Rose[7] also quotes Simeone's experiments on guinea pigs which demonstrated sympathetic motor supply to the seminal vesicles. Although ectasia of the vesicles was most frequently observed in our patients with lesions between T-7 and T-12 (splanchnic outflow) which would support Rose's[7] view, ectasia occurred also with lesions above and below this outflow, a fact which militates against full acceptance of exclusive sympathetic supply of the spermatic vesicles.

Pereira's[2] interpretation of the vesiculograms was preferred to that of Tucker and his associates,[3] because Pereira's[2] description appeared to be more succinct. Yet, one must concede that the range of normal may be wider than the one here presented (27 per cent); this is especially true for the difficult differentiation between "normal" and "hypoplasia," where the borders are probably fluctuating and which, if added, would increase the range of normal to approximately 51 per cent.

No explanation can be offered for the appearance of reflux from one ejaculatory duct to the other (fig. 2, *D*) in 2 cases or for the presence of dye in the prostatic lumina (fig. 2, *C*) of a third patient. All three patients had an upper motor neuron lesion of the external urethral sphincter, i.e. the sphincter was not flaccid Another point is hard to understand, namely that in the presence of obvious morphologic changes such as ectasia of the vesicle and/or ampulla of the vas, cyst of the vesicle and secondary atrophy of the vesicles, no pus cells could be found in the washings with two exceptions, and even then the white blood cell count was rather low.

No correlation seemed to exist between the type of the spermatocystogram and the following factors: level and extent of injury, age of patient, duration of nerve lesion and quality of testicular biopsy. The latter point is interesting because atrophy of the male adnexa could be understood in the absence of testicular function.[8]

The relative paucity of demonstrable sperm in the washings confirmed again[1] that the spermatic vesicles are no receptacles or storing space for sperm. Therefore, spermatic washings of paraplegic patients are unfortunately not suited for use in artificial insemination which in many cases is the desired goal. There was a complete lack of correlation of spermatic washings with testicular biopsy.

The testicular biopsy findings of this series failed to confirm a previously

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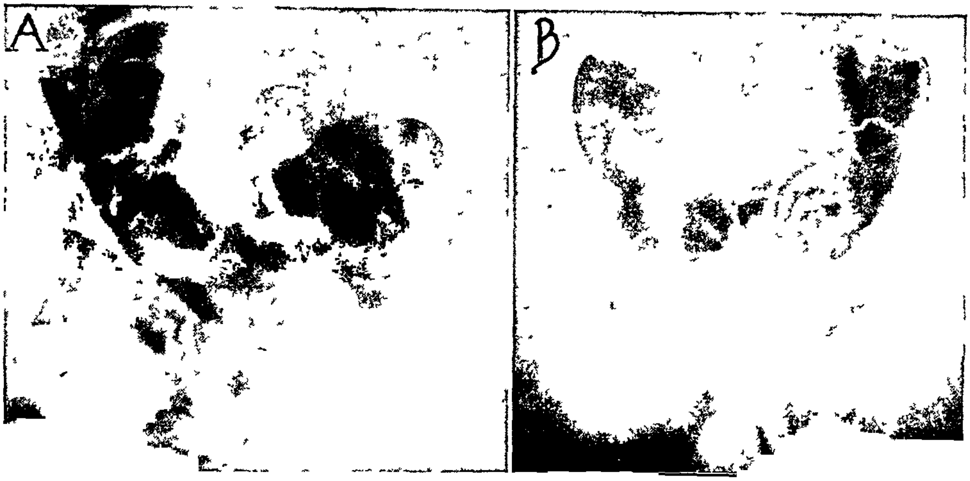
[7] Rose, S S · An investigation into sterility after lumbar ganglionectomy. Brit. Med. J, 1: 247–250, 1953.

[8] Herbut, Peter A · Urological Pathology. Philadelphia · Lea and Febiger, 1952.



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[4] Boreau, J., Elbim, A., Hermann, P., Vasselle, B. and Flua, R.: L'épididymographie. La Presse méd., **59**: 1406-1407, 1951.

[5] Boreau, J., Vasselle, B. and Jagailloux, S.: Étude radiologique des voies génitales normales et pathologiques de l'homme. La Presse méd , **61**: 1-4, 1951.

[6] Retief, P. J M.: Physiology of micturition and ejaculation. South African Med. J., **24**: 509-512, 1950.

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GANTRISIN ACETYL (ACETYL SULFISOXAZOLE) IN TREATMENT OF URINARY TRACT INFECTION

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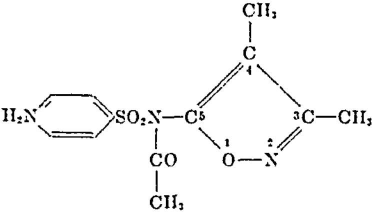
Prior prediction of the development of new resistant bacterial strains has now unfortunately come true. As a result of the intensive, almost universal, administration of the sulfonamides and antibiotics, some infectious diseases have well nigh been eradicated. Recently, however, we and others have noted a striking increase in the number of drug resistant organisms in cultures from the urinary tract, and are again encountering cases of fulminating and fatal infection so commonly seen before the advent of the sulfonamides. These observations make it incumbent to find and to test clinically new therapeutic agents.

The authors have been given the opportunity to employ and evaluate a new sulfonamide, which was provided under the experimental designation Ro 2-6222.* This compound is acetylated sulfisoxazole (gantrisin acetyl) with the acetylation having taken place at the N^1 position. The structural formula of acetyl sulfisoxazole is as follows:



It is a white, crystalline, odorless, tasteless powder, m.p. 193–194 C. (corr.). The molecular weight is 309.

PHARMACOLOGY

Acetyl sulfisoxazole has antibacterial and toxic properties very similar to those of sulfisoxazole (gantrisin).†

In white mice the tolerated dose was found to be at least 10 gm./kg. Chronic toxicity studies were carried out in rats. A dose level of 0.5 per cent (in terms of sulfisoxazole) in the diet produced no loss of weight. With 1.15 per cent acetyl sulfisoxazole (the molecular equivalent of 1 per cent sulfisoxazole) there was essentially no change in the weight of the females but approximately a 10 per cent decrease in the males.

Blood counts taken before treatment and 4 weeks after treatment with acetyl sulfisoxazole showed no significant effects on red blood counts, white blood counts, or hemoglobin determinations in rats at a dose level of 0.575 and 1.15

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* The experimental drug was supplied through the courtesy of Dr. Leo A. Pirk of Hoffmann-La Roche Inc., first under the code designation Ro 2-6222 and later under the name of Gantrisin Acetyl (generic designation acetyl sulfisoxazole).

† The authors are indebted to Dr. Emmanuel Grunberg and Dr. Lowell Randall of Hoffmann-La Roche Inc. for the chemotherapeutic and pharmacological data.

per cent in the diet. At a level of 2.3 per cent there appeared to be a slight depression of all blood constituents.

Blood level studies of acetyl sulfisoxazole and sulfisoxazole measured in rats by the Bratton-Marshall method showed that the drugs give comparable blood levels at the respective concentrations in the diet.

The effect of acetyl sulfisoxazole on the rabbit kidney was studied by the daily administration of 1000 mg./kg. for a maximum of 30 days, as compared with control animals treated with like amounts of sulfisoxazole, sulfadiazine, and a triple sulfonamide mixture, consisting of equal parts of sulfadiazine, sulfamerazine and sulfamethazine. On histological examination, the kidneys of rabbits treated with acetyl sulfisoxazole and sulfisoxazole failed to exhibit signs of renal damage as contrasted with those treated with sulfadiazine and the triple sulfonamide mixture. It would seem that acetyl sulfisoxazole resembles sulfisoxazole in regard to the absence of intratubular crystallization and subsequent renal damage.

CASE MATERIAL

Acetyl sulfisoxazole was administered to 62 consecutive unselected patients suffering from urinary tract infection. There were 47 men and 15 women, varying in age from 25 to over 80; most were over 50 years old.

For the purpose of this study, the patients were divided into 2 groups: ambulatory private patients and hospital ward patients. The former group consisted of 40 ambulatory patients with, for the most part, simple urinary infections; many had recently been discharged from the hospital following suprapubic prostatectomy. There were 23 patients with a single organism on the primary urine culture and 10 with mixed infection. In the cases of mixed infection the effect of the drug on each organism was observed and separately tabulated (table 1). Seven cases were omitted because of incomplete follow-up or non-cooperation.

The hospital ward group was made up of 22 patients, most of whom had just undergone prostatic or renal operations. These cases, in contrast to the ambulatory group, were complicated by foreign bodies, such as drainage tubes and catheters, and in 1 case by residual renal calculi. There were 6 patients with a single organism on the primary urine culture and 6 with mixed infection. The effect of the drug on each organism was separately observed and tabulated (table 2). Ten cases were excluded because of incomplete follow-up.

DOSAGE

Each patient received 1.77 gm.* of acetyl sulfisoxazole 4 times daily, a total daily dose of 7.08 gm. (12 tablets). Treatment was continued until a bacteriological reversal had occurred or until the inefficacy of the drug became apparent. The total dosage ranged from 100 to 400 tablets which were given either in 1 uninterrupted course or in 2 courses at about a week's interval.

CRITERIA FOR CURE

The results were evaluated solely on the basis of bacteriological findings. Cures were assumed when the urine repeatedly showed no white blood cells and when

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* 1.77 gm. of acetyl sulfisoxazole and 1.5 gm. of sulfisoxazole are equi-molecular amounts.

TABLE 1. *Ambulatory private patients, 33 cases*

Organisms	Treated	Cured	Failed
B. coli and coliform	20	11	9
B. proteus	14	10	4
B. lactis aerogenes	8	2	6
B. pyocyaneus	2	0	2
Non-hemolytic staph. albus	2	1	1

TABLE 2. *Hospital ward patients, 12 cases*

Organisms	Treated	Cured	Failed
B. coli and coliform	11	1	10
B. proteus	1	1	0
B. lactis aerogenes	6	1	5

2 consecutive urine cultures were negative. Some patients in whom there was no bacteriological cure showed decided clinical improvement; these were tabulated as failures.

TOXICITY

Generalized pruritic dermatitis characterized by a mild course occurred in 4 patients. Medication was immediately discontinued and the eruption subsided within a few days. Three of these patients had received penicillin prior to treatment with acetyl sulfisoxazole and at least one of them had been proved sensitive to penicillin. In the fourth patient a rash had developed from sulfisoxazole while in the hospital. The subsequent administration of acetyl sulfisoxazole was experimental.

No other untoward reactions were observed.

RESULTS

In a series of 62 patients suffering from urinary tract infection, the best results were obtained in ambulatory patients whose infection was due to B. proteus, B. coli and coliform organisms. The presence of foreign bodies, such as drainage tubes, catheters and calculi, greatly interfered with the effectiveness of the drug, as is evident from the results obtained in the hospital ward cases (tables 1 and 2). Acetyl sulfisoxazole appears as safe as sulfisoxazole and similar to it in therapeutic efficacy.

SUMMARY

Gantrisin acetyl (acetyl sulfisoxazole) was found to have a favorable therapeutic effect similar to that of gantrisin (sulfisoxazole) in cases of urinary tract infection caused by B. proteus, B. coli and coliform organisms Gantrisin has a bitter taste which can be masked only with great difficulty. Gantrisin acetyl has the advantage of being tasteless and, therefore, can be administered in liquid form particularly to children and to those adults who are unable to swallow tablets.

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South Central—San Antonio, Texas, October 17–19, 1955
Southeastern—Hotel Jung, New Orleans, La , March 21–23, 1955
Western—Hotel del Coronado, Coronado, Calif., January 24–27, 1955

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ELEVENTH RIB, EXTRAPLEURAL APPROACH TO KIDNEY

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Since the level of the kidney varies considerably among individuals the incision which will afford the best exposure will vary also. A kidney whose pedicle is below the rib cage may be easily accessible with a subcostal, lumbar incision, and one that lies higher may have sufficient mobility so that when freed up it can be drawn into the incision to allow a proper view. A certain number, however, are so placed that their pedicle and upper pole are difficult to expose because they are so high up under the thoracic cage.

The extent to which any kidney is so protected is not readily apparent if judged only from an anteroposterior x-ray. This is because only the dorsal portion of the ribs behind the kidneys are well shown. As these ribs turn to form the lateral and anterior portions of the rib cage, they become foreshortened and indistinct. Since the surgical approach is from nearly an oblique angle, it is the oblique x-ray which shows the projection of the ribs as they will be encountered at operation (fig. 1, *1*). One notes in examining such x-rays that the oblique downward and forward sweep of the lower ribs carries them diagonally across the kidney region. Also, the anterior portions of the ribs are visible and serve to emphasize the extent to which they cover the kidney. In some instances the twelfth rib is found to lie posterior to the surgical approach, whereas the eleventh rib crosses the kidney obliquely near its midportion. These facts help to explain why through a subcostal incision one often finds a kidney previously thought readily accessible, lying under the rib cage and difficult to expose. By resecting the eleventh rib one gains direct access to the renal hilum.

The incision for any renal operation should be selected after due consideration of the extent to which the bony cage overlies the kidney. The degree of fixation of the kidney from inflammation or previous operations, as well as the requirements of exposure for a given procedure, will also influence this choice. With routine use of a subcostal incision for all renal operations some are made unnecessarily difficult or hazardous, and some cannot be properly completed. Removal of some portion of this bony rib cage will improve access to the renal area.

Resection of the twelfth rib has become widely accepted since it permits several centimeters higher exposure than the subcostal incision. Resection of the tenth rib as advocated by Chute, and by Leadbetter, gives excellent complete exposure. The fact that the pleura is transversed has been shown to make little real difference in complications or difficulties of management. Also the procedure described by Nagamatsu and which enjoys considerable popularity, where the twelfth rib is resected along with small segments of the tenth and eleventh, gives comparable exposure yet is extrapleural.

The twelfth rib incision has been most widely used because of its simplicity

Read at annual meeting American Urological Association, New York, N. Y., June 3, 1954.

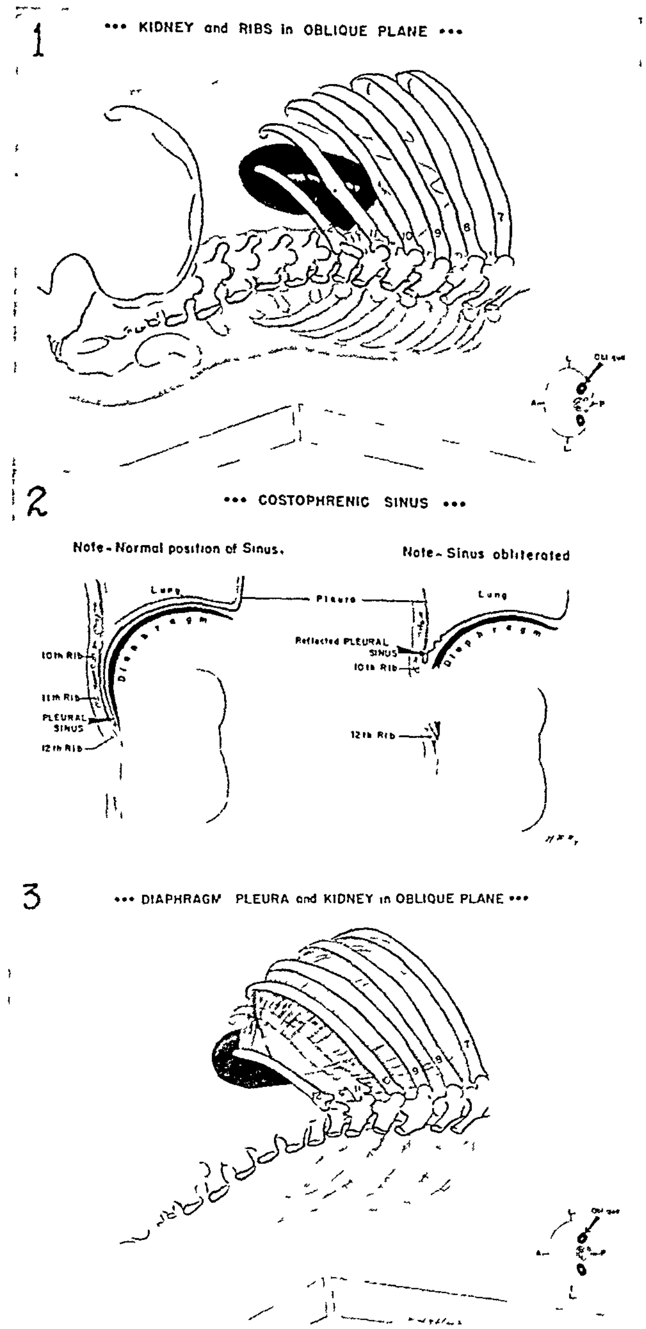
1
••• KIDNEY and RIBS in OBLIQUE PLANE •••
7
8
9
10
11
2
••• COSTOPHRENIC SINUS •••
Note- Normal position of Sinus.
Note- Sinus obliterated
Lung
Pleura
Diaphragm
10th Rib
11th Rib
PLEURAL SINUS
12th Rib
Lung
Diaphragm
Reflected PLEURAL SINUS
10th Rib
12th Rib
3
••• DIAPHRAGM PLEURA and KIDNEY in OBLIQUE PLANE •••
7
8
9
10

Fig. 1

and similarity to the subcostal approach. Removal of the eleventh rib, if done extrapleurally, is practically a corollary of this. It is very similar except in detail. When the exposure obtained from the twelfth rib incision would not be sufficiently high and yet there seems insufficient need for a transthoracic or Nagamatsu incision, removal of the eleventh rib extrapleurally may be the logical intermediate step. Removal of the eleventh rib has been avoided by many because it involved a transthoracic approach. It is, however, possible to remove the eleventh rib and remain extrapleural. This is done by releasing the pleural envelope beneath the rib bed and allowing it to retract upward.

If either the eleventh or twelfth rib is removed, it should be realized that the diaphragm attaches not only to the tip of the eleventh rib but to the tip of the twelfth and posteriorly to the fascia below it. The pleura, lying upon this diaphragm, extends down to form the costophrenic sinus, in the narrow juncture of diaphragm with the rib cage. The anterior and posterior surfaces of pleura in this sinus are in apposition as the lung does not descend this far in normal respiration (fig. 1, *2*). This envelope lies immediately beneath the periosteum of the ribs upon the curving surface of the diaphragm and is loosely adherent to each. It also extends down to, and often below the twelfth rib. Consequently if this rib is resected, care must be taken in dissecting through the posterior portion of the rib bed not to enter it. It is possible, however, once the rib has been removed to identify the pleura and diaphragm in this area. With some care the posterior diaphragm attachments can be cut allowing it to retract upward. The tip of the pleura lying upon it can be bluntly freed allowing it to retract upward also. Once this is done the posterior angle of the wound will open, giving a considerable increase in exposure. The gain from releasing these attachments in the posterior angle of the wound is very real.

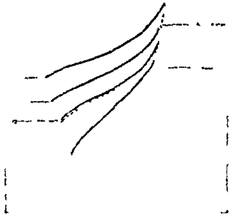
FIG. 2. Kidney incisions

If the eleventh rib is removed an entirely similar situation prevails except that the pleural margin extends farther anterior to cross the rib at about the junction of the anterior and middle thirds. It also extends downward behind the twelfth rib so that it must be freed bluntly from the posterior surface of this rib (fig. 1, *3*). By cutting the diaphragm attachments, as well as by releasing the pleural sac, both will retract upward to give the same wide posterior angle to the wound, and the same wide exposure, though now at a higher level.

We claim no particular originality for this procedure. Certainly resection of the eleventh rib is a standard thoracic approach and the extrapleural principle has been widely used, particularly for sympathectomies. Hudson recently reported a series of adrenalectomies by a somewhat similar procedure involving the same principles. Our interest in this incision has not been held primarily by details of procedure, but rather by the principle of a family of incisions which will give adequate exposure depending on the anatomical location of the kidney, and the

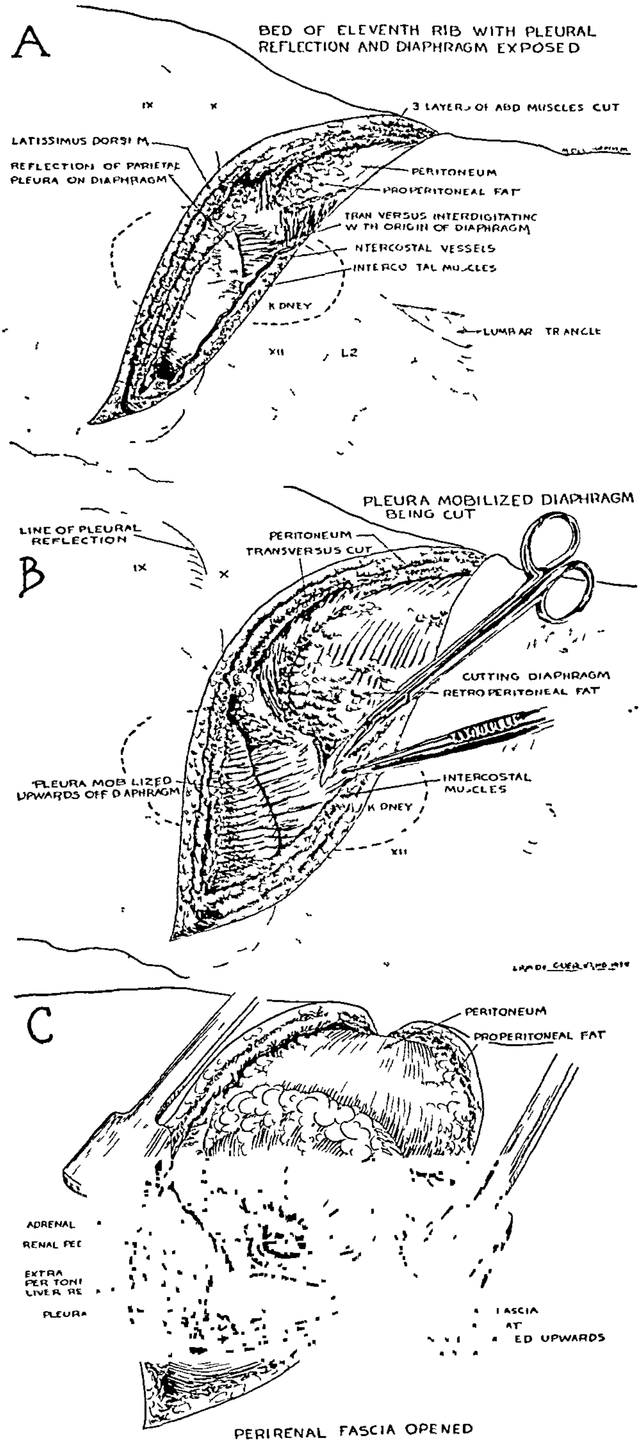
A
BED OF ELEVENTH RIB WITH PLEURAL REFLECTION AND DIAPHRAGM EXPOSED
IX
X
3 LAYERS OF ABD MUSCLES CUT
LATISSIMUS DORSI M.
REFLECTION OF PARIETAL PLEURA ON DIAPHRAGM
PERITONEUM
PROPERITONEAL FAT
TRANSVERSUS INTERDIGITATING WITH ORIGIN OF DIAPHRAGM
INTERCOSTAL VESSELS
INTERCOSTAL MUSCLES
KIDNEY
LUMBAR TRIANGLE
XII
L2
B
PLEURA MOBILIZED DIAPHRAGM BEING CUT
LINE OF PLEURAL REFLECTION
IX
X
PERITONEUM
TRANSVERSUS CUT
CUTTING DIAPHRAGM
RETROPERITONEAL FAT
PLEURA MOBILIZED UPWARDS OFF DIAPHRAGM
INTERCOSTAL MUSCLES
KIDNEY
XII
C
PERITONEUM
PROPERITONEAL FAT
ADRENAL
RENAL PED
EXTRA PERITONI LIVER RE
PLEURA
FASCIA
AT
ED UPWARDS
PERIRENAL FASCIA OPENED

FIG 3

pathological condition under treatment. The eleventh rib incision is the logical intermediate. That it can be done extrapleurally increases its usefulness (fig. 2).

The method we have used is as follows: The patient is intubated and placed in the usual lateral position. An incision is made along the eleventh rib from behind its angle and extending anteriorly onto the abdominal wall. The forward extent varies with the size and obesity of the patient and the width of exposure desired. If during the operation a wider view is found necessary, one or both recti muscles can be transected and the incision extended even into the opposite lower quadrant. The eleventh rib is then cleaned of overlying muscles to behind its angle. The periosteum is stripped from its surface and an elevator insinuated around the rib near its anterior end. This stripping is started anterior to the pleural margin, and only when well established is it carried posteriorly. In this way the pleura is not damaged. The rib is removed to behind its angle. The anterior abdominal muscles are next transected to expose the peritoneum and Gerota's fascia. At the tip of the eleventh rib bed the diaphragmatic fibers crossing to the twelfth rib now become apparent and the anterior pleural margin can be identified (fig. 3, *A*). In some instances this is more readily apparent than others. The fibers of the diaphragm are transected from before backwards nearly to the pleural margin, and as this is done the pleura becomes tensed and more clearly defined (fig. 3, *B*). By blunt finger dissection the pleura is freed from the posterior surface of the twelfth rib. Any fibrous attachments holding the lower edge of the pleural margin now become fairly plain and can either be cut carefully under vision or bluntly freed with a finger. The pleura retreats progressively upward as this is done, and as the freeing is completed, it disappears behind the tenth rib. Moist packs are then placed along the margins of the wound and a self-retaining rib spreader employed (fig. 1, *C*). One now obtains an unobstructed oblique view across the right or left upper quadrant, the center of which is at the renal hilum

Wound closure is like that of a twelfth rib incision except that the severed diaphragm attachments are re-approximated by a series of interrupted mattress sutures Care is taken not to pass these through the pleural margin which lies upon it.

We have used this incision in 36 cases of the types shown in table 1 There has been no mortality. The complications have been 1 case of wound infection and 2 cases of pneumothorax requiring aspiration.

TABLE 1 *Types of cases*

Renal cyst	14
Renal tumor	5
Renal calculi	12
Renal tuberculosis	1
Renal artery aneurysm	1
Adrenalectomy	3
Total	36

On several occasions the pleura has been opened inadvertently; in each it has been closed either immediately or at the completion of the operation and the pleura aspirated. If for any reason a satisfactory airtight closure was not possible a small thoracotomy tube on water-seal or suction for 48 hours has been used to prevent pneumothorax.

The increased width and height of exposure gained by this incision allow safe, easy dissection of the renal vessels. Thus in many nephrectomies in which a mass ligation of the pedicle might otherwise have been necessary, because of improved exposure, individual ligation of the vessels could be safely performed. The view obtained of the upper pole also allows careful dissection of the adrenal from the kidney and performance of adrenalectomy with some facility.

When previous operations upon the kidney have caused fixation or extensive scars, it may be more practicable to use a high incision such as this through normal tissue, particularly as this will afford direct access to the region of the hilum. Pain during healing is difficult to assess, but it is our impression that it is less than with a lumbar incision which necessitates cutting considerably more muscle. Since the intercostal nerve is exposed and lies on the lower margin of the field it is easily preserved.

In removing renal tumors, access to the region of the great vessels is sufficient that Gerota's fascia can be stripped from the diaphragm, and the renal and perirenal tissue together with lymph nodes can be cleanly removed.

SUMMARY

Removal of the eleventh rib and reflecting the underlying pleura upward intact is a practical procedure. Very wide exposure of the renal pedicle and upper pole is obtained. With a very high kidney or one bound by scar and difficult to access, or where a wide exposure is required, this incision should be considered.

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PYELOPLASTY UTILIZING A MODIFIED URETERONEOPYELOSTOMY

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The modification of the classical ureteroneopyelostomy evolves from the excision of an elliptical flap of renal pelvis incorporating the ureteropelvic junction, and its re-implantation into the most favorable site for unimpeded drainage of the renal pelvis This method permits correction of strictures at or below the ureteropelvic junction

Ureteroneopyelostomy was the method used by Kuester in 1892 in performing the first successful pyeloplasty In 1935 Lubash modified this method by splitting the end of the ureter, and suturing the flaps to the pelvic mucosa Miller, in 1951, incised the severed ureter past the point of stricture, or beveled the ureter prior to its re implantation in the most dependent portion of the renal pelvis In 1951 Gjessing modified the method of Lubash by splitting the proximal ureter creating two straps of ureteral tissue, which are drawn through the neopyelostomy site, and carried out through lateral slit incisions, and sutured to the outer wall of the renal pelvis

Despite the excellent results following ureteroneopyelostomy reported by Quinby, Walters, and others, there appears to be a reluctance on the part of urologists to sever the ureter from the renal pelvis This feeling probably stems from the thought that there will be a marked disturbance in peristalsis with resulting stasis, that would defeat the purpose of the plastic procedure

Ormond had two failures requiring re operation In each instance the ureteral stump projected into the renal pelvis and acted as a valve Beer observed the same condition, and corrected it by fulguration of the stump by way of nephroscopy Ormond, Quinby and Walters emphasize the need for accurate approximation of ureteral and pelvic tissues

The etiology of ureteropelvic junction obstructions has been discussed in detail in Deming, Gibson, etc Needless to say, a complete pelvi ureterolysis and calibration of the ureteropelvic junction are mandatory No one method of pyeloplasty is suitable for all types of obstruction, and that method best suited to the individual case determined at the time of surgical intervention Ureteroneopyelostomy is particularly suitable for the correction of high ureteral insertion, and in the preservation of essential aberrant renal vessels

SELECTION OF CASES

We believe that whenever possible functioning renal tissue should be preserved Sargent has stated that hydronephrosis tends to be bilateral, and that at a later date the apparently sound kidney will undergo hydronephrotic change

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* Read at annual meeting, Western Section of American Urological Association, Victoria, B C April 19-22, 1954

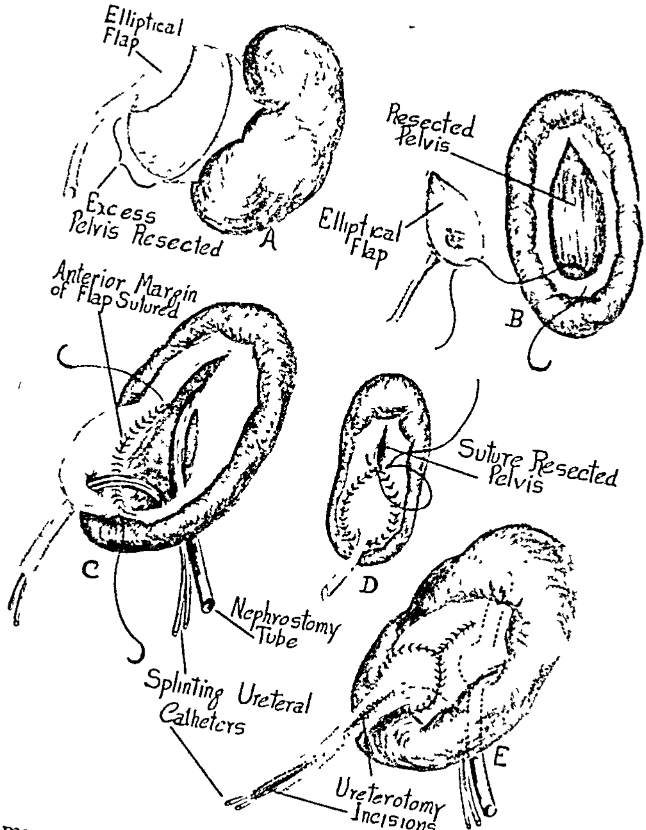

FIG. 1. Semidiagrammatic illustration of surgical technique. *A*, elliptical flap of pelvis with ureter; *B*, placement of initial anastomotic suture; *C* and *D*, completion of anastomosis; *E*, ureterotomy incisions.

necessitating plastic correction. This fact is noted in four of the 6 cases here reported. Gibson in discussing the theory of renal counterbalance stresses this point, and favors the plastic correction of the hydronephrotic kidney even though at its initial evaluation it does not appear that it can perform 25 per cent of its total function. Deming stresses the need for conservation of aberrant renal vessels. On occasion it is impossible to know whether or not a hydronephrotic kidney can be salvaged as a useful organ. If after careful evaluation a reasonable hope for success is present, I believe the surgeon is justified in performing a pyeloplasty.

SURGICAL TECHNIQUE

The kidney is completely mobilized by a combination of blunt and sharp dissection performed through an adequate lumbar incision. The proximal portion of the ureter and renal pelvis are then carefully mobilized, all fibrous bands or investing fascial veils being released by sharp dissection. Small aberrant renal blood vessels are ligated and severed. The obstructed ureteropelvic junction is carefully evaluated, and if ureteroneopyelostomy is decided upon, the following procedure is utilized. An elliptical incision (fig. 1, *A*) is made in the renal pelvis beginning 0.5 cm. from the inferior margin of the ureteropelvic junction, and terminating 2 cm. superior to the ureteropelvic junction. The excess renal pelvis is then resected leaving a 0.5 cm. margin at the inferior border of the renal hilum, and 0.5 to 1 cm. margin at the superior border to facilitate closure. The ureteropelvic junction is then calibrated, using 12F and 14F woven bougies, any stricture or valve formation to be corrected later. A 16F, 5 cc Foley catheter, and two 5 or 6F ureteral catheters are then introduced through an inferior minor calyx to the renal pelvis. The ureter with its elliptical flap of pelvic tissue is then carried in front of the aberrant vessels, or in their absence, to the most dependent portion of the renal pelvis. Using a 0000 chromic suture (fig. 1, *B*) the inferior margin of the elliptical flap is sutured to the inferior margin of the renal pelvis. About 20 cm. of suture material is allowed to remain free following the initial tie to permit suturing the posterior aspect. The anterior margin of pelvis and flap are then approximated with a running suture (fig. 1, *C*), incorporating all layers. At this point, if a stricture or valve formation seemed to be present at the time of calibration of the ureteropelvic junction, an adequate incision is made through all layers of the ureteropelvic junction and ureter on the medial aspect (fig. 1, *E*), opposite the site of anastomosis. The two splinting ureteral catheters are then introduced into the ureter a distance of 15–20 cm. The free end of the suture material is then used to approximate the posterior margin of the elliptical incision with that of the pelvis. Anastomosis of the pelvic flap completed, the sutures are tied (fig. 1, *D*), and one strand retained for closure of the resected pelvis. The tip of the Foley catheter is directed into the superior calyx, and the balloon inflated with 2 cc of water. Closure of the renal pelvis is completed with the remaining strand of 0000 chromic suture. The kidney is suspended in favorable position by Kelly triangular sutures tied over the twelfth rib. Sometimes it is necessary to place a mattress suture of 0 chromic through the inferior pole of the kidney and quadratus lumborum muscle in order to obtain sufficient lateral deviation of the lower pole of the kidney. Gerota's fascia is approximated to the quadratus lumborum muscle with interrupted 00 chromic sutures in a modified type of Deming nephropexy. The region of the renal pelvis is left open to permit favorable drainage. A Penrose drain is introduced into the parapelvic area posterior to the lower pole of the kidney, and a second drain along the mobilized portion of the ureter. The incision is closed in layers, and the nephrostomy and splinting ureteral catheter fixed to the skin with 0 silk sutures.

POSTOPERATIVE MANAGEMENT

The nephrostomy tube is irrigated only if definite impairment of drainage is evident. The Foley balloon is decompressed in 48 hours. Solvent solutions are not used in the immediate postoperative phase, feeling that their irritant action outweighs their usefulness. Where ureterotomy incisions have been utilized the splinting ureteral catheters are left undisturbed three to six weeks depending on the length and caliber of the stricture to be corrected. In the absence of ureterotomy incision, beginning at 72 hours, the ureteral catheters are shortened 1 to 2 cm. daily. Prior to the removal of the nephrostomy tube an antegrade urogram is made to evaluate the patency of the ureteroneopyelostomy, and any evidence of calculus formation. The Penrose drains are left undisturbed until there is a marked diminution in drainage, then they are shortened daily. Ambulation is inaugurated on the fifth to seventh postoperative day, pelvic circulation having been stimulated previously by passive exercise of the lower extremities at frequent intervals. The immediate medical management consists primarily of adequate supportive measures; hyaluronidase 150 TR units daily; and appropriate antibiotic therapy. Calibration of the ureteropelvic junction is done only if there is question of developing obstruction.

CASE REPORTS

Case 1. R. G. T., a man aged 42, complained on admission of left flank pain with no elevation of temperature. Excretory urography showed bilateral hydronephrosis, more advanced in the left kidney. Cystoscopy with ureteral catheterization disclosed 20 cc residual urine in the right renal pelvis and 50 cc in the left renal pelvis. Indigo carmine appeared in the right renal urine in 10 minutes with fair concentration, and from the left in 15 minutes with good concentration. Retrograde urograms revealed bilateral hydronephrosis secondary to ureteropelvic junction obstruction, more advanced in the left kidney. On July 8, 1949, the left kidney was explored surgically, and the obstructing element proved to be extrinsic, due to a large aberrant vessel to the lower pole combined with an investing veil of fascia. The ureter was transplanted in front of the aberrant vessel by the technique described. Two 7F ureteral splinting catheters were used. The splinting ureteral catheters were removed on the fourteenth postoperative day. The following day retrograde urograms showed no appreciable retention and the nephrostomy tube was removed. The nephrostomy site was dry in 24 hours. Six weeks following surgery the urine was negative and the patient had returned to work.

Case 2. F. G., a woman aged 60, complained on admission of left flank pain. Excretory urograms revealed left hydronephrosis secondary to ureteropelvic junction obstruction (fig. 2, *A*). On December 21, 1950 surgical exploration revealed two large aberrant vessels to the lower pole to be the main source of obstruction. Ureteropyeloneostomy was performed in the manner described preserving the aberrant vessels. Splinting ureteral catheters were removed on the sixteenth postoperative day, and the nephrostomy tube on the seventeenth postoperative day. The nephrostomy site was dry in 48 hours. A retrograde ureteropyelogram (fig. 2, *B*) shows an excellent recovery.

Case 3. A girl aged 2½ years had had recurrent attacks of left flank pain and fever. Excretory urography showed left hydronephrosis secondary to ureteropelvic junction obstruction (fig. 3, *A*), and the right renal pelvis seemed to be undergoing a similar change but to a lesser degree. On February 7, 1951, surgical exploration revealed a high ureteral insertion into the renal pelvis with the ureter bound to the pelvis by a veil of fibrous tissue. Following liberation of this element by sharp dissection, calibration of the ureteropelvic junction through a high pyelotomy incision disclosed obstruction to the introduction of an 8F catheter. A linear incision 1 cm. in length through the ureteropelvic junction permitted the introduction of the 8F rubber catheter 4 cm. into the ureter where a secondary ureteral obstruction was encountered. A linear incision 1 cm. in

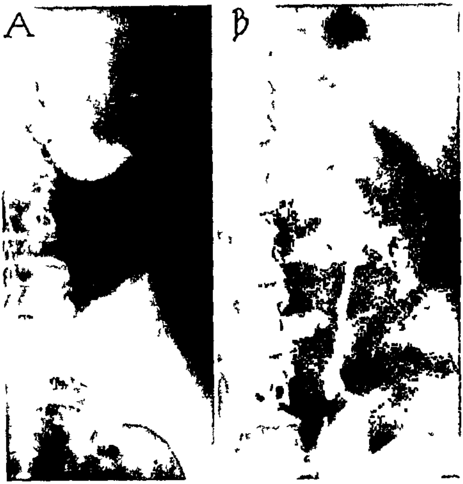

FIG 2 Case 2 *A*, preoperative left hydronephrosis *B*, ureteropyelogram 3 months postoperatively

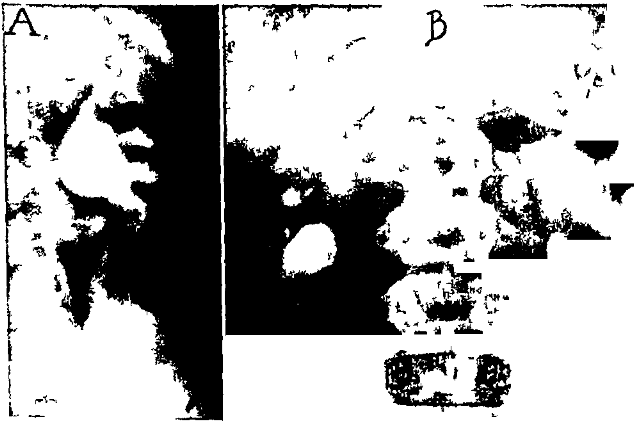

FIG 3 Case 3 *A*, excretory urogram showing left hydronephrosis *B* urogram 3 years postoperative shows return to normal of left kidney, and suggestion of obstruction in right ureteropelvic junction

length permitted the passage of the ureteral catheter beyond this point without further evidence of obstruction The remainder of the operation was then completed in the manner previously described The splinting catheter was removed in 21 days and the nephrostomy tube 3 days later The nephrostomy site closed promptly Excretory urograms (fig 3, *B*) performed in

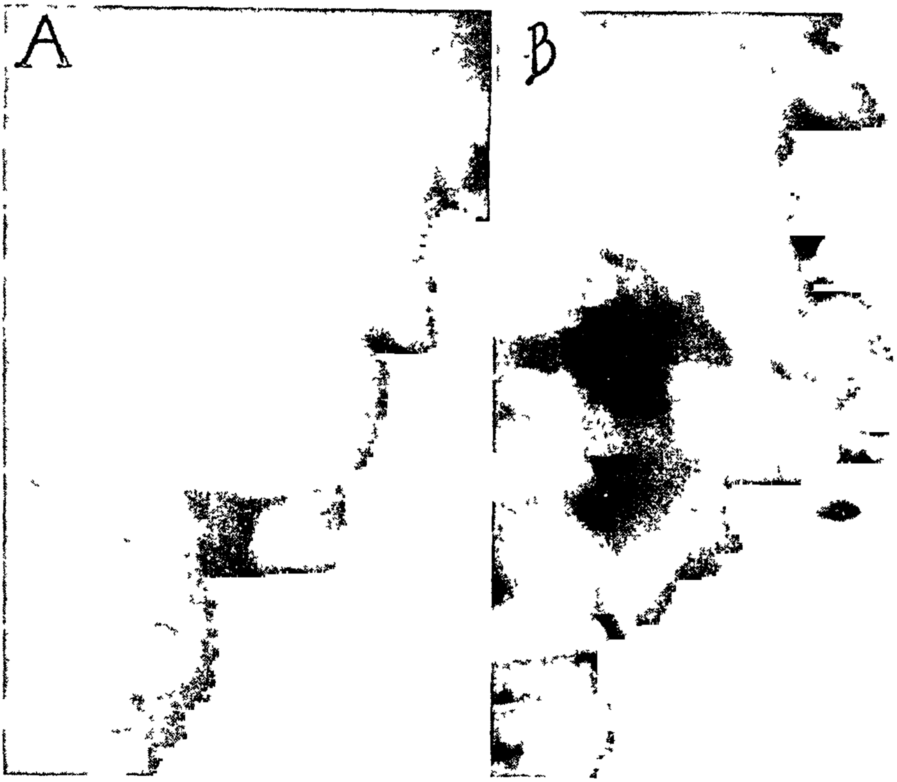

FIG. 4 Case 4 *A*, Left hydronephrosis *B*, 16 months postoperatively, return to normal of calyceal configuration

March 1954 reveal a normal left calyceal system, and a suggestion of uretero-pelvic junction obstruction in the unoperated kidney.

Case 4. D. L., a boy aged 4½ years, was a doctor's son who had been subject to recurring attacks of colicy left flank pain, nausea, vomiting, and low grade fever. Excretory urography (fig 4, *A*) revealed left hydronephrosis, secondary to ureteropelvic junction obstruction. On August 2, 1951, at the time of surgical correction, the source of the obstruction was proven to be an aberrant renal vein and artery supplying a relatively small amount of renal parenchyma. These vessels were ligated and severed, and ureteroneopyelostomy performed to provide a more favorable angle of drainage. The patient was released from the hospital on the twenty-first postoperative day with the nephrostomy site dry. A retrograde urogram (fig. 4, *B*) 16 months later shows a return to normal of the calyceal system.

Case 5. S. M., a girl, aged 3 years, was seen in consultation because of a large mass in the right flank that was thought to be a Wilms's tumor. Cystoscopy with retrograde urograms revealed a complete obstruction in the mid right ureter, and advanced left hydronephrosis secondary to ureteropelvic junction obstruction (fig. 5, *A*). On February 6, 1952, through a small flank incision, the right renal pelvis was marsupialized and pyelostomy drainage established. On February 8, 1952, left ureteroneopyelostomy was performed. This procedure was complicated by the presence of two large aberrant vessels to the upper pole that prevented adequate mobilization of the kidney. The obstructing

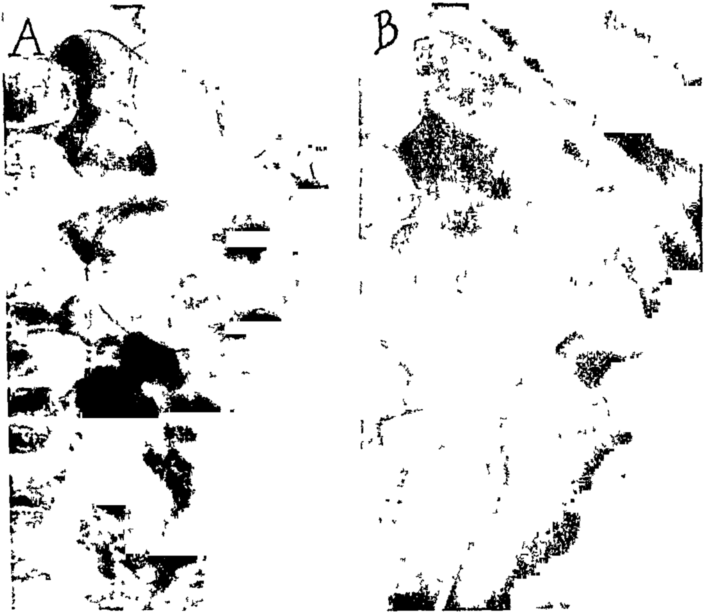

FIG. 5 Case 5 Solitary kidney *A*, left hydronephrosis. *B*, ureteropyelogram 1 year postoperative

element at the ureteropelvic junction was thought to be the left ovarian artery and vein. A moderate narrowing below the ureteropelvic junction was incised. An 8F rubber catheter was used as a ureteral splint. On April 2, 1952, a right nephrectomy was performed. The splinting ureteral catheter was removed in 3 weeks and the nephrostomy tube the following day. This child has continued to improve in all respects and the retrograde urogram (fig. 5, *B*) performed 1 year later shows an excellent return to normal.

Case 6. F. G. V., a man aged 73 years, had a right nephrectomy performed in April 1949 because of a functionless hydronephrotic right kidney secondary to ureteropelvic junction obstruction, the obstructing aberrant renal vessels being demonstrated at the time of surgery. There was no evident left renal disease In the same year a transurethral resection of the prostate gland was performed. Vague left flank discomfort developed in February 1953, and became localized and more severe during the latter part of April 1953. On May 5, 1953, a retrograde urogram (fig. 6, *A*) revealed an obstruction at the left ureteropelvic junction with advanced intra- and extrarenal hydronephrosis. Indigo carmine failed to appear in 45 minutes. The presence of an aberrant renal vessel was predicated on the basis of this finding at the time of right nephrectomy. Preoperative nonprotein nitrogen was 79 mg. per cent. On May 31, 1953, a left ureteroneopyelostomy was performed. Two large aberrant vessels to the lower

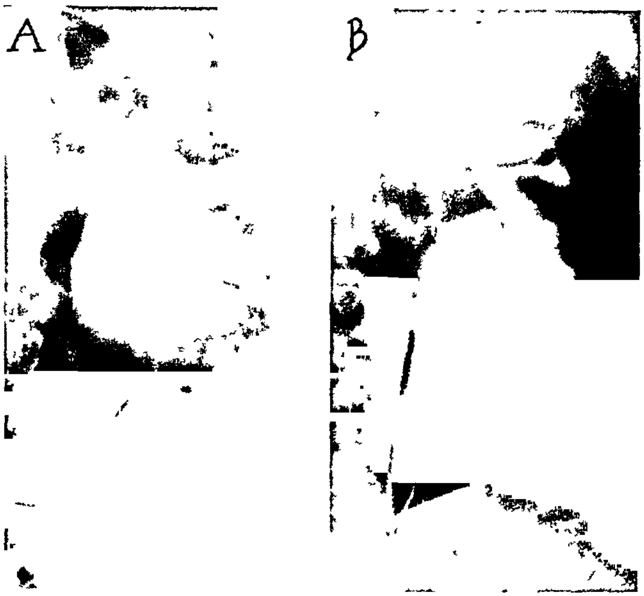

FIG. 6. Case 6. Solitary kidney. *A*, left hydronephrosis. *B*, *retrograde urogram* 9 *months' postoperative*.

pole appeared to be major factors in the ureteropelvic junction obstruction. There was no intrinsic stricture of the ureteropelvic junction. Splinting catheters were removed on the eighteenth postoperative day, the nephrostomy tube 3 days later, following a satisfactory urogram. The nephrostomy site was dry in 24 hours. Nine months following pyeloplasty the nonprotein nitrogen is 36 mg. per cent. The left renal pelvis accepts an 8F bulb catheter easily, and the residual renal urine is 4 cc. Indigo carmine appears in 7 minutes with excellent concentration. Figure 6, *B*, retrograde urogram using 8 cc of 40 per cent skiodan, shows an excellent return to normal of the calyceal system, and practically no retention of medium on the 15 minute delayed upright film.

DISCUSSION

Complete pelvio-ureterolysis and calibration of the ureteropelvic junction are essential for successful pyeloplasty. Resection of redundant renal pelvis was performed in all cases, and where indicated aberrant vessels were preserved. Stricture at, or below the ureteropelvic junction was corrected by the Davis intubated ureterotomy technique. The elliptical flap lends itself particularly well to this method, in so far that the ureterotomy incision does not interfere with the line of anastomosis at the site of re-implantation. In anastomosis of the pelvic flap to the resected pelvis the suture incorporates all layers of the pelvic wall without tension.

The two splinting ureteral catheters maintain the ureter and ureteropelvic junction in good alignment, and permit constant ureteral drainage of the renal pelvis with less tendency to produce pressure necrosis. The nephrostomy tube allows immediate drainage, and may be left in situ as a permanent method of drainage if the situation so demands. Nephropexy further enhances a favorable alignment of ureter and pelvis, and facilitates the change of nephrostomy tubes if this be necessary The parapelvic drains are left relatively undisturbed to prevent pooling of urine seeping from the pelvic incision, which would predispose to scar tissue formation and subsequent obstructive uropathy We feel that prompt closure of the nephrostomy site is an excellent indication of a successful result Postoperative calibration of the ureteropelvic junction was performed in two of the cases reported and then only at a later date

Cases 1, 3, 5, 6 fulfill the tenets laid down by Hess for obligatory, conservative renal surgery

SUMMARY

The technique of pyeloplasty utilizing an original modification of ureteroneo-pyelostomy has been described in detail, and its use advocated in selected cases of ureteropelvic junction obstruction

This method permits the use of the Davis intubated ureterotomy for correction of strictures at or below the ureteropelvic junction

Resection of redundant renal pelvis, splinting ureteral catheters, nephrostomy drainage, and nephropexy are advocated in all cases where this method is used

Six consecutive cases are cited with favorable end results

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SURVEY OF UROLITHIASIS IN UNITED STATES

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As a background for the study of urolithiasis, a questionnaire was sent to all members of the American Urological Association and all members of the Western Section who were not members of the national organization. This report is a summary of the survey. Three hundred and forty replies were received from the national group and 49 replies from the Western Section group.

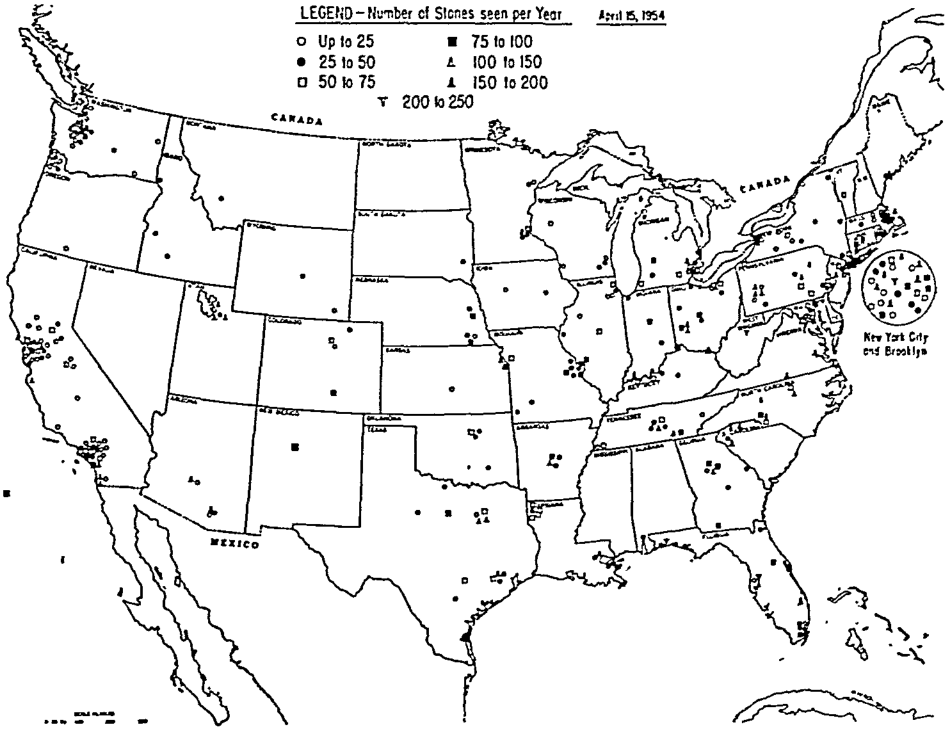

FIG. 1. Map showing geographic distribution of number of calculi seen yearly in the United States.

In answer to the first question, "How many patients suffering from renal and ureteral calculi do you see each year?" the range was from 10 to 250, with an average of 61.6 patients among 290 men reporting in the national group. A range of 5 to 200 patients a year was seen in the Western Section group among 42 reporting with an average of 44.7. Figure 1 is a map showing the distribution of renal and ureteral calculi seen yearly in the United States.

In order to indicate the geographical distribution of calculi the country was arbitrarily divided into sections made up of the states as follows:

Read at annual meeting, Western Section of American Urological Association, Victoria, B. C. April 19–22, 1954.

Far West
California
Oregon
Washington
Nevada
Hawaii

West
Colorado
Nebraska
Kansas
Utah
Idaho
Montana
Wyoming

Middle West
Michigan
Ohio
South Dakota
North Dakota
Illinois
Iowa
Indiana
Minnesota
Wisconsin

Southwest
Texas
Arizona
New Mexico
Oklahoma

Northeast
Massachusetts
Rhode Island
Maine
New Hampshire
Vermont

East
New York
Connecticut
Pennsylvania
New Jersey
Delaware

South and Southeast
Arkansas
Virginia
Washington D. C.
Georgia
Tennessee
Louisiana
West Virginia
Florida
Maryland
Alabama
North Carolina
South Carolina
Kentucky
Missouri
Mississippi

The national geographic distribution of number of patients seen yearly was:

Far West	40.0	East	61.3
Southwest	60.6	Northeast	61.7
West	69.	South and Southeast	75.4
Mid-West	57.	Average	61.6

The number of patients with renal and ureteral calculi seen in the last 5 years was reported as follows:

National	*Western Section*
Range of 15 to 1000	Range of 5 to 1000
Average—251.6	Average—181

The geographic distribution of national group of patients seen in five years was:

Far West	177.5	East	234.
Southwest	203.4	Northeast	286.
West	231.	South and Southeast	380.7
Mid-West	261.	Average	251.6

The percentage of patients having recurrent calculi was reported as:

National	*Western Section*
Range of 1–50%	Range of 2–75%
Average—13.7%	Average—14.4%

Geographic distribution of percentage of recurrence:

Far West	11.7	East	12.7
Southwest	15.8	Northeast	14.4
West	12.8	South and Southeast	14.7
Mid-West	13.9	Average	13.7

Concerning the incidence of urolithiasis the reports were:

National		*Western Section*	
Increasing	93	Increasing	18
Decreasing	86	Decreasing	23
No change	39	No change	7

Thus an average of 61.6 patients with calculi are seen yearly per urologist with the greatest number 75.4 seen in the South and Southeast and the fewest 40.0 in the Far West. The percentage of recurrent cacluli was 13.7 per cent for the national survey with the highest percentage of recurrence reported in the Southwest and Southeast and lowest in the Far West. The opinion was slightly in favor of an increase in the incidence of urolithiasis in recent years. Better and earlier care of vesical obstruction was felt to be a factor in decrease of cystolithiasis. A few urologists mentioned that the incidence of nonopaque calculi is higher than generally noted.

Regarding the incidence of recurrence the reports were:

National		*Western Section*	
Decreasing	202	Decreasing	87
Increasing	30	Increasing	2
No change	13	No change	5
Don't know	12	Don't know	4

The general comments on these questions were that earlier and better drainage, better control of infection by the use of antibiotics, earlier and more scientific treatment and follow-up and attention to the diet were cutting down the recurrence of stones.

Concerning the value of stone analyses the following figures were obtained:

National		*Western Section*	
Great value	136	Great value	14
Little value	152	Little value	24
No value	22	No value	5

The chief comments were that analyses are helpful in treatment of stones due to metabolic causes, the cystine and uric acid stones, and also helpful to lesser degree in treatment of calcium oxalate and phosphate stones by diet (Schorr's regimen) and change of urinary pH.

Regarding questions as to the measures of value in preventing recurrence of stones, table 1 represents a summarization of answers.

Thus it was felt that the elimination of obstruction, infection, and the high daily intake of water were the most important measures in preventing recurrence of stones. The administration of an appropriate diet, depending upon the analyses of the removed stone, was considered of great value by many men, especially for cystine and uric acid stones. The eradication of foci of infection particularly in the prostate was emphasized by a few men. The performance of calycectomy, the adequate removal of the original stone and correction of obstruction at the ureteropelvic junction as well as the correction of metabolic disorders and the use of estrogens to increase urinary citrate excretion were stressed by a few men as further measures to prevent recurrence. Early ambulation or frequent change of position was considered helpful where stone was due to immobilization and recumbency. While 22 men felt that hyalouronidase was of value in the treatment and prevention of calculi several other men reported no success with its use.

Concerning the value of dissolution of calculi by irrigation the following opinions were obtained.

National		*Western Section*	
Of great value	8	Of great value	3
Of little value	125	Of little value	15
Of no value	63	Of no value	14

TABLE 1

National

Measures of value in preventing recurrence

	Marked	Some	None
(1) Forcing water	204	67	6
(2) Acid ash diet or urinary acidification with drugs .	48	111	30
(3) Alkaline ash diet	21	113	66
(4) Limiting milk intake and low calcium diet	42	86	77
(5) Low oxalate intake	28	91	53
(6) Low phosphorus intake	26	89	57
(7) Antacids (amphojel, etc.).	47	67	38
(8) Eliminating infection	241	30	4
(9) Eliminating obstruction	283	22	0
(10) High vitamin A intake	46	74	46
(11) Other			
Low purine diet 7, estrogen 5			
Hyalouronidase 17, early ambulation P.O 10			

Western Section

	Marked	Some	None
(1) Forcing water	30	14	1
(2) Acid ash diet	2	27	5
(3) Alkaline ash diet	2	17	19
(4) Limiting milk intake	7	18	11
(5) Low oxalate intake	2	19	17
(6) Low phosphorus intake	8	17	9
(7) Antacids (amphojel, etc).	4	19	7
(8) Eliminating infection	31	11	1
(9) Eliminating obstruction	37	8	0
(10) High vitamin A intake	4	18	13
(11) Other			
Increased activity 2			
Hyalouronidase 5, low purine diet 2			

Preferable solution:

National		*Western Section*	
Suby's	78	Suby's	30
Versene	15	Versene	1
Other	1% Phosphoric acid	3	
	Acetic acid	2	

Several men felt that irrigations were only of value in bladder calculi and alkaline bladder encrustations or in recurrent renal calculi where the patient has a residual stone fragment following surgery with a nephrostomy tube in place.

The spontaneous dissolution of calculi was observed in 169 cases by 159 men in national group and in 9 cases by 9 men in Western Section group. The factors of importance were considered to be: forcing fluids, loose encrustation of the stone, early ambulation and in some cases use of a high acid ash diet and change from inactive to active life.

Concerning the eradication of renal calculi by diet, 21 replied yes and 157 no in the national group; yes 4 and no 33 in Western Section group.

Eight men had success with an alkaline ash diet for cystine stones and alkaline ash plus low purine diet for uric acid stones. Eleven men had success with a low phosphorus diet with acidification of the urine and forcing fluids. (Five men reported on success with the Schorr regimen.) Three men felt that high vitamin A intake was helpful, 4 men that administration of ammonium chloride was beneficial and 1 man a low calcium diet.

In regard to the relationship of urolithiasis to the following factors these observations were reported.

National		*Western Section*	
Age		*Age*	
Commonest	30–50 years	Commonest	20–50 years
Next	50–75 years		
Rare	Below 20		
Sex		*Sex*	
Predominantly male	77	Male (3–1)	12
Predominantly female	6	Male (2–1)	6
No relation	25	Male	15
Male (2–1)	30	Even	2
Male (4–1)	5		
Diet		*Diet*	
None	33	None	8
Questionable	9	Heavy eaters	2
Ulcer diet	4	High calcium intake	1
Excess purine	4	Excess purine	2
Alkaline ash	4		
Acid ash	5		
Water		*Water*	
Inadequate intake	111	Inadequate intake	14
Associated with excessive perspiration	9	High intake of hard water	2
None	9		
Questionable	5		
Excess intake of:		*Excess intake of:*	
Milk	45	Milk	11
Fruit juice	26	Fruit juice	2
(a) none	36		
Excess intake of other:		*Excess intake of other:*	
Rhubarb	4	Alkalis (Sippy diet)	3
Carbonated beverages	5		
Alkalis (Sippy diet)	4		
Oxalates and calcium	2		
Coffee, cocoa for oxalates	2		

National

Race

Predominantly white	60
Rare in Negro	26
None	15
Increased in Italians	5
Common in Jews	2
None in Eskimos	1
None in Bolivia	1
Rare in American Indian	1
Rare in Polynesians	1

Occupation

None	67
Sedentary	9
Those associated with excessive perspiration and low fluid intake	4

Geographical location

None	20
Florida	4
New England	2
New York	3
Southwest	2

Metabolic Disturbances

None	15
Gout	11
Cystinuria	11
Hyperparathyroidism	11

Climate

None	27
Hot dry	33
Humid tropical	14
Seasonal variation	7
Temperate	4

Hypervitaminosis

Excess vitamin D	5
None	44
Possibly in pregnancy	1

Other

With ulcerative colitis	4
Recumbency	4
Stress	4
Pregnancy patients on large doses of estrogen	1
Nervous influences	2
Familial incidence	2

Western Section

Race

Predominantly white	21
Scandinavian	2
Chinese	3

Occupation

None	8
Sedentary	1
Laborer	5
Farmer	2
Excessive perspiration	3

Geographical location

Desert area	3
South Pacific	5
Southern California	2

Metabolic Disturbances

None	4
Gout	3
Cystinuria	2
Hyperparathyroidism	2

Climate

None	6
Hot dry	8
Humid tropical	1
Seasonal variation	2
Temperate	1

Hypervitaminosis

Excess vitamin D	2
None	6

Other

Pregnancy	3
Recumbency	7
Idiopathic hypercalcinuria	1
Familial incidence	1

In summary it appears to our commentators that the commonest age group for stones is 30–50 years They occur predominantly in the male sex and white

TABLE 2. *Predisposing or associated factors in stone formation*

National		
	Range %	Average %
Obstruction	2–100%	41.5
Infection	5–100%	47.00
Recumbency	2–50%	10.00
Hyperparathyroidism (216 replies)	0.0–15.0%	.79
a. Sectional incidence of hyperparathyroidism		
Far West	.50%	
West	.76%	
Mid-West	.72%	.79%
Southwest	.74%	
Northeast	1.05%	
East	.47%	
South and Southeast	1.28%	
Other metabolic factors		
Gout or hyperuricemia	4%	
Cystinuria	1%	
Drug—sulfa crystalluria	1%	
No ascertainable known causes for urolithiasis	25.95%	50%

Western Section		
	Range %	Average %
Obstruction	1–100%	25.8
Infection	3–100%	38.4
Recumbency	1–50%	9.0
Hyperparathyroidism	0.0–5.0%	.73

National		
	Cases	Men
b. Hyperparathyroidism	86	44
Associated with typical blood chemistry changes	62	24
Normal blood chemistry	7	4
Surgically proven parathyroid adenoma	119	50

Western Section		
Gout or hyperuricemia cystinuria	5%	
Drug—sulfa crystalluria	1%	
No ascertainable known causes for urolithiasis	14–100%	60%

race. Diet is considered of no questionable influence by the highest percentage of those urologists answering. An inadequate intake of water is a big factor in stone formation, as is an excess intake of milk and, to a lesser degree, fruit juices. Occupation and geographic location appear to have no relationship to stone formation. Metabolic disturbances such as gout, cystinuria and hyperparathyroidism are important. Stones form more commonly in a hot dry climate. A few men in the South and Southwest note an epidemic of ureteral stones, particularly in young people with no previous urinary difficulty, during the hot summer months. This coincides with the seasonal variation in the incidence of stones seen in other parts of the country in hot weather. Hypervitaminosis is no more frequent a factor in stone formation than recumbency or stress or ulcerative colitis. One man commented that metabolic factors alone don't account for calculi, there must be a localizing factor also.

Concerning the percentage of stone cases presenting certain predisposing or associated factors, the replies are indicated in table 2.

Thus obstruction and infection were considered as very significant associated factors in urolithiasis in a great percentage of cases, up to 100 per cent by some men and in a very low percentage (2 per cent) by others. Foci of infection (especially prostatitis), were considered significant by a few men. Recumbency was considered a factor in 10 per cent of cases. An average incidence of 0.79 per cent was reported for hyperparathyroidism. While only 44 men replied that they had seen 86 cases of hyperparathyroidism, a total of 119 cases of surgical proven parathyroid adenoma associated with stone formation were reported as seen by 50 men of the national group in their total experience. A total of 15 cases were reported seen by 13 men in the Western Section group. However, 126 urologists, many with long and extensive experience, stated that despite search they had never encountered a case of hyperparathyroidism. Countering this observation a few men stated that with more intensive search through the wider use of laboratory facilities more cases of hyperparathyroidism would be uncovered.

Gout was considered a factor in about 4 per cent and cystinuria in 1 per cent of stone cases. A great percentage of the reporting urologists feel that there was no known cause for stone formation in from a small per cent to 95 per cent of their cases. The opinion was expressed that there is probably no single cause for stone in any case, that stone formation is the result of the operation of several factors combined, the relative importance of each factor being usually in doubt.

Concerning the predominating type of stones (composition) seen in your area the replies were:

	Calcium Phosphate	Calcium Oxalate	Mixed	Urate & Uric Acid	Carbonate
National					
Far West	30	13	3	5	1
West. .	8	6	4	2	0
Southwest	8	9	1	3	1
Mid-West	33	26	0	8	6
East	35	43	12	17	6
Northeast	10	14	0	2	1
South and Southeast	57	32	5	12	7
National total .	154	143	25	49	22
Western Section .	18	11	13	5	3

The commonest type of stone is calcium phosphate with calcium oxalate a close second. Several men reported that the commonest situation with regard to urolithiasis in their practice was that a patient presented himself with a small ureteral stone (often of oxalate composition) which he passed or was extracted and usually he never had another one. Thus at the time of examination more ureteral stones were found than renal. If a stone recurred it was usually of phosphatic composition.

DISCUSSION

The results of a survey by questionnaire of the members of the American Urological Association and the Western Section on the problem of urolithiasis is presented. This study does not lend itself to rigid conclusions although a fairly representative group of replies was obtained from every section of the country.

Patients with stones form a large proportion of most urological practices. An average of 60 a year are seen per urologist. The percentage of recurrence is approximately 14 per cent. While the incidence of urolithiasis appears to be remaining the same, the incidence of recurrence is decreasing because of the institution of earlier and better drainage, the use of antibiotics, attention to fluid intake and diet and perhaps newer dietary regimens, etc. Stones analyses were considered of value largely in the metabolic group, the cystine and uric acid calculi.

Forcing water daily, elimination of obstruction and infection were felt to be the chief measures in preventing recurrence. The acid and alkaline ash diets, limiting milk, phosphorus and oxalate intake and high vitamin intake were considered of moderate value by most observers. Early ambulation was considered of value in stones of recumbency. It was general opinion that attempts at dissolution of calculi by irrigations were of little or no value.

A rather large number of cases of spontaneous dissolution of calculi, 169 by 159 men, was observed. The eradication of stones by diet was reported as quite unsuccessful. Concerning miscellaneous factors, stones were considered to be predominantly more frequent in the male sex of the white race, in the age group 30–50 and frequently associated with an inadequate intake of water. Forty-five men felt an excess intake of milk and 26 men felt that an excess intake of fruit juices were definite factors in stone formation. Thirty-six men commented that an excess intake of these substances was no factor in stone formation. Five men felt an excess intake of carbonated beverages (coca cola) was a factor in stone formation.

Most observers felt that occupation and geographical location were not factors in the United States. Fifteen men felt that metabolic disturbances were not a factor while 11 men felt that gout, cystinuria and hyperparathyroidism were significant factors. A hot, dry climate was considered predisposing to stone formation by many, and an epidemic of small ureteral calculi was noted in the summer months, particularly in the South and Southwest.

Of interest is that 4 men noted an association with ulcerative colitis and 4 with stress.

Obstruction was considered an associated factor in 41.5 per cent of cases, infection in 47 per cent, recumbency in 10 per cent in the national group. An average incidence of .79 per cent was reported for hyperparathyroidism. One hundred and nineteen cases of surgical proven parathyroid adenoma were seen by 50 men but many urologists of experience reported never seeing a case of hyperparathyroidism. Gout was considered a factor in 4 per cent of cases and cystinuria in 1 per cent. In a very large percentage of cases, no known cause for stone formation was noted. This is a significant observation and indicates the need for more interest in the study of the etiology of stone.

The commonest type of stone seen appears to be of calcium phosphate composition with calcium oxalate, uric acid and stones of mixed composition following.

The authors wish to thank those members of the American Urological Association and Western Section of the AUA who made this study possible by replying to the questionnaire sent to them.

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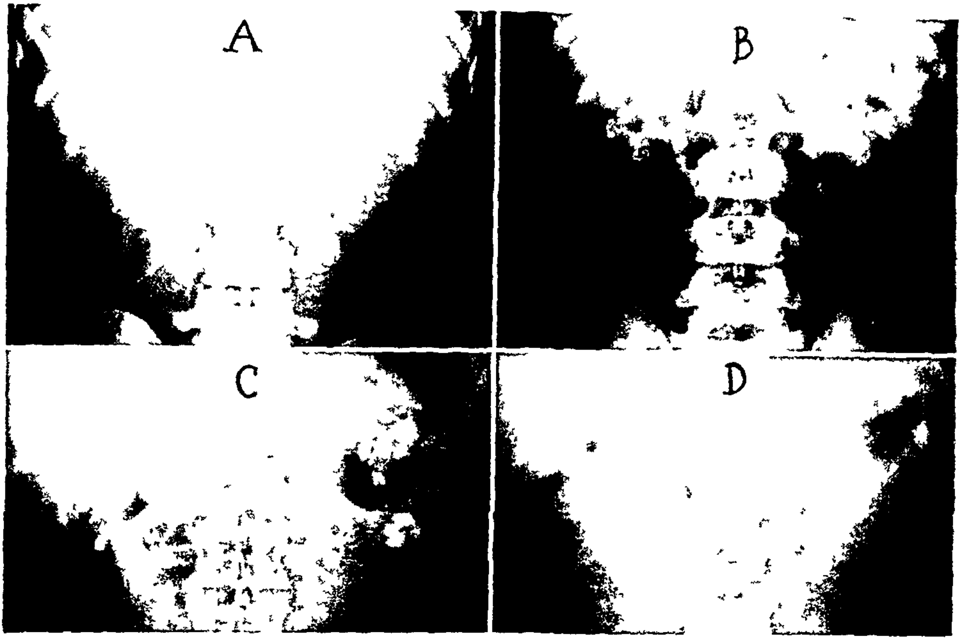

FIG. 1. *A*, radiograph of sister, now 16 years of age, showing nephrocalcinosis. *B*, excretory urogram of 11 year old brother. *C*, radiograph of 40 year old father *D*, radiograph of 10 year old brother showing early nephrocalcinosis

it was agreed that such a procedure might be necessary in the future in the event of obstructive or destructive changes.

The patient was discharged from the hospital on a regimen of ammonium mandelate, vitamin tonic and a regular diet. Unfortunately we have not been able to follow her but presumably her medications were not continued for long. We understand she has been completely asymptomatic and apparently healthy. A recent plain film of the abdomen taken elsewhere shows no change in her renal picture.

Our interest in this case was recently rekindled by the referral of an 11 year old boy with nephrocalcinosis. He proved to be the younger brother of the girl whose case we have been discussing. He entered the University of California Hospital on January 21, 1954 with a diagnosis of Bright's disease which was made 5 years prior to entry. This apparently cleared after 3 months.

Three months prior to entry intermittent bilateral flank pain developed and soon thereafter the boy passed some small urinary stones. Several of these were recovered and reported as calcium phosphate.

Examination showed a pale, small, but not dwarfed boy, with no remarkable physical findings except for residual wasting of the tibial muscles and a left foot drop from a previous attack of poliomyelitis.

Urinalysis showed pH of 6, a specific gravity of 1.008 and a moderate calciuria. Urine cultures were negative.

There was no x-ray evidence of rickets and the renal pattern of calcification was similar to that of the sister but without separate stones in the pelves or ureters (fig. 1, *B*). Electrolyte studies yielded normal results. The phenolsulfonphthalein output was 55 per cent in 1 hour Here, then, is a case of nephrocalcinosis without either rickets or dwarfism and, unlike his sister, the patient showed absolutely no electrolyte imbalance or urinary tract infection

The history of Bright's disease and prolonged bed rest associated with poliomyelitis are possibly significant etiologic factors, but again they would only serve to tell part of the story A logical presumption is that this patient, too, at some time in the development of this condition might have demonstrated hyperchloremic acidosis but that that particular phase had subsequently corrected itself with only the unusual renal findings to mark the previous pathological process It is also logical to assume that his sister also passed through the hyperchloremic stage, the condition having spontaneously corrected itself, and that she would now probably show a completely normal electrolyte panel

There have been constant socio economical factors precluding complete investigation of these interesting children However, we did manage to obtain abdominal plain films on the rest of the family, viz , the mother, father, a sister and a brother Of these, the father aged 40 and the brother aged 10 also were found to have nephrocalcinosis (figs 1, *C* and *D*) but apparently have been at least relatively healthy and asymptomatic to date

Mortensen, Emmett, and Baggenstoss in June 1953 published a review on various aspects of the 91 cases of nephrocalcinosis reported up to that time They stated that nephrocalcinosis was found in one out of every 3,000 autopsies and comprised approximately 0 5 per cent of nephrolithiasis They found no racial or familial tendency Our discovery of 4 members of one family with x-ray findings of nephrocalcinosis, one of whom also had hyperchloremic acidosis, suggests an hereditary factor in the disease

We wish to gratefully acknowledge the kindness of Dr J Park Tuttle of Reno, Nevada for obtaining the radiographs of the father and younger brother in this report and that of Dr Gilbert Gordan of the Department of Internal Medicine, University of California Hospital for his helpful advice in preparing this presentation

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PERINEPHRITIS PLASTICA

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Vest and Barelare[1] recently reported 4 cases of an entity they labeled "periureteritis plastica," in which the ureter was encased in a thick fibrous envelope to such a degree that symptoms and clinical findings of ureteral obstruction resulted. No pathogenesis was demonstrated but it was postulated that infection was the most likely cause. In one of their cases the kidney as well as the ureter was encased in fibrous tissue. A review of the literature does not reveal reports of similar findings. Recently, we encountered a process which is reported because of the striking pathological changes and its resemblance in many ways to periureteritis plastica.

CASE REPORT

A 40-year old Negro entered the hospital on the medical service with the chief complaint of postprandial epigastric pain of 10 months' duration. At first the pain was relieved to some extent by food and alkalies but later it became unremitting and more severe, with radiation into the left flank. There was a weight loss of 15 pounds during the 6 months prior to hospital admission. Past history, regarded as reliable, included no episodes of severe trauma and no episodes of epigastric or flank pain prior to the onset of the present illness. Nocturia once nightly had been present for the preceding five months without any associated urinary tract symptoms. Fifteen years previously the patient received "sulfa drugs" for "gonorrhea." Five years later he received 16 "606 shots" for a lesion on the glans penis. For the past 12 years there had been recurrent episodes of a generalized dermatitis.

The patient was well developed, lean and cachectic, with a generalized vesiculopapular dermatitis. The liver edge was smooth and slightly tender, extending 4 cm. below the right costal margin. A tender, firm mass that was palpable in the left upper quadrant did not move with respiration. Inguinal, right axillary and submental lymph nodes were enlarged up to one centimeter in diameter, firm, and movable.

Complete blood count and blood urea nitrogen values were within normal limits. The urine contained five to ten white blood cells and three to four trichomonads per high power field in a centrifuged specimen.

A roentgen examination of the upper gastro-intestinal tract revealed coarse rugal folds in the stomach. Barium enema studies were normal. Excretory urography showed caliectasis and reduced renal function on the left side. The renal outline, particularly that of the upper pole, was indistinct. The right kidney appeared normal.

At cystoscopy the right ureter was easily catheterized and the right kidney

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Read at annual meeting, Western Section of American Urological Association, Victoria, B. C. April 19–22, 1954.

[1] Vest, S. A. and Barelare, B.: J. Urol., 70: 38, 1953.

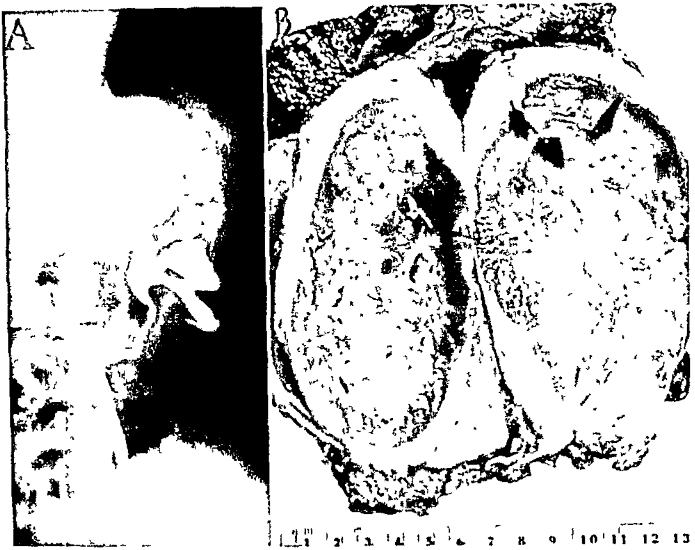

FIG. 1. *A*, retrograde pyelogram made with Braasch bulb, again showing caliectasis and absence of renal outline. *B*, gross specimen. Kidney has been split showing thick, fibrous envelope. Cut surface of spleen and portion of diaphragm lie superiorly. Remaining structures lie behind and are not visible.

excreted indigo carmine promptly and in good quantity. A urine specimen was not obtained from the left kidney because the examiner was unable to pass a ureteral catheter more than one centimeter on that side. A retrograde urogram (fig. 1, *A*), made with a Braasch bulb on the left side, showed normal renal architecture on the right and confirmed the changes seen on the left in the intravenous study. It failed to demonstrate obstruction. There was delayed and poor quantitative excretion of indigo carmine from the left side.

A culture of bladder urine yielded a light growth of Streptococcus pyogenes and diphtheroids. Urine from the right kidney was sterile. Cultures of 24-hour urine collections for Mycobacterium tuberculosis were sterile.

An aortogram showed a double renal artery on the left side but no abnormalities in the intrarenal circulatory pattern. Again the left renal outline was indistinct.

A bland diet with interval feedings of milk and cream relieved the epigastric pain although the flank pain continued. Biopsy of the right axillary and submental lymph nodes showed only chronic inflammation. A diagnosis of dermatitis herpetiformis was made by the dermatologist. The patient was treated with sulfapyridine and remission of the skin lesions ensued. He was transferred to the urological service with a presumptive diagnosis of carcinoma of the left kidney.

On December 22, 1953, the left kidney was approached through a thoracoabdominal incision. A hard mass was encountered which encased the kidney and adrenal and partially encased the spleen. The tail of the pancreas, splenic flexure of the colon and a portion of the diaphragm were adherent to the periphery of this mass. Many hard lymph nodes measuring one to two centimeters in diameter were palpable around the renal pedicle. The remainder of the abdominal organs including the stomach and duodenum were normal to palpation. These findings so strongly suggested an extensive neoplasm that the entire mass was excised *en bloc*, including the kidney, adrenal, spleen, tail of pancreas, splenic flexure of colon, segment of diaphragm and the regional lymph nodes. The cut ends of the colon were united by end-to-end anastomosis. The capsule of pancreas was loosely approximated over its cut surface. Postoperative recovery was entirely uneventful except for the development of a retroperitoneal abscess requiring surgical drainage on the eighteenth postoperative day. Culture of the abscess yielded Staphylococcus aureus. The wound healed without further difficulty, the patient making a complete recovery. When last seen 13 weeks postoperatively, the patient was feeling well and was gaining weight.

PATHOLOGY

Examination of the mass removed at surgery showed the kidney completely and the spleen partially surrounded by a dense, white, fibrous envelope measuring one to two centimeters in thickness (fig. 1, *B*). This fibrous envelope had completely replaced the perirenal fat and stripped from the kidney with difficulty, leaving a finely granular surface. A thin margin of fibrous tissue measuring one to two millimeters in thickness was seen to surround the renal pelvis and to extend upward along the infundibula to the calyces. The upper ureter included in the specimen appeared normal. The renal parenchyma was pale but not other-

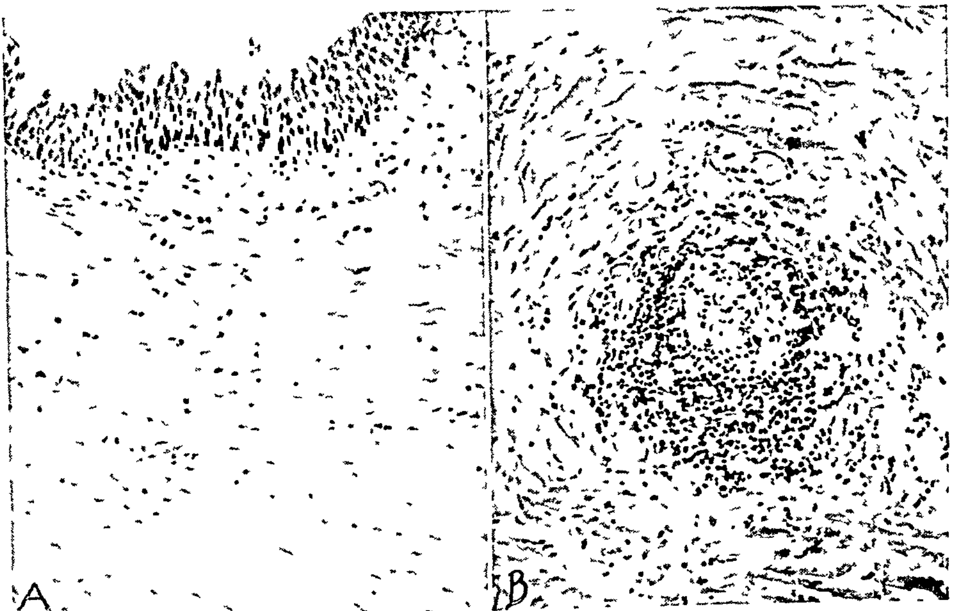

FIG 2. *A*, showing adult collagenous connective tissue surrounding renal pelvis *B*, showing one focus of round cell infiltration within fibrous envelope Cells are predominantly lymphocytes with a few plasma cells and occasional granulocyte

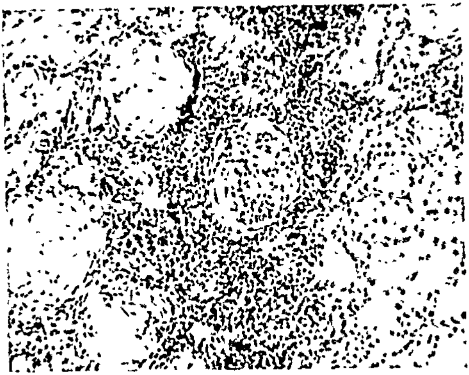

FIG. 3. Showing periphery of renal cortex with hyalinized glomeruli on left, round cell infiltration in center.

wise remarkable. The posterior surface of the spleen was covered with this same fibrous envelope. The anterior surface of the spleen was normal. The tail of the pancreas, splenic flexure of the colon, and a segment of diaphragm were adherent to the fibrous envelope. Eighteen lymph nodes around the renal pedicle were firm and measured one to two centimeters in diameter. With the exception of the kidney and the lymph nodes, the removed organs showed no intrinsic abnormalities.

On microscopic examination the fibrous envelope surrounding the kidney and the renal pelvis (fig. 2, *A*) consisted of adult collagenous connective tissue. There were scattered foci of round cell infiltration in the fibrous envelope (fig. 2, *B*). Sections were stained for bacteria but no organisms were detected. Sections through the junction of the fibrous envelope and the renal parenchyma showed infiltration with lymphocytes, a few plasma cells, and an occasional granulocyte (fig. 3). With van Gieson's stain this zone showed connective tissue fibrils extending into the renal cortex and many hyalinized glomeruli. The renal capsule could not be identified. With the exception of this peripheral zone of round cell infiltration and fibrosis, the renal parenchyma was normal. The lymph nodes showed only chronic inflammatory changes. The other organs were normal.

DISCUSSION

The most striking feature of this case was the complete replacement of the perinephric fat by a dense, fibrous envelope which completely surrounded the kidney and adrenal and was attached to neighboring structures. Microscopically this envelope consisted of collagenous connective tissue which contained a few scattered foci of lymphocytes and plasma cells. At the interface between renal cortex and fibrous envelope, infiltration with round cells and hyalinization of glomeruli were prominent. The renal parenchyma deep to this zone was normal, suggesting that the entire process originated extrarenally and involved the periphery of the renal cortex secondarily. The presence of round cell infiltration and the microscopic characteristics of the lymph nodes pointed to an inflammatory reaction, the cause of which was not apparent. Tissue sections stained for bacteria failed to demonstrate organisms. Urine cultures showed only light growths of Streptococcus pyogenes and diphtheroids; 24-hour urine cultures for Mycobacterium tuberculosis were sterile.

An exhaustive history failed to reveal anything suggesting a perirenal hematoma or a perinephric abscess. Examination of the kidney failed to show any intrinsic disease (such as peri-arteritis nodosa) which might produce a spontaneous hematoma. Furthermore, blood pigments were not found in the microscopic sections. Barium enema and careful examination of the excised colon showed no abnormalities.

In none of Vest and Barelare's cases was there a history of severe renal or perirenal disease. There was no evidence that either the ureter or kidney was the primary source of the disease. In their second case, they describe a fibrous perirenal mass which seems similar to the fibrous envelope around the kidney in the present case. Although the ureter was free of disease in our case it is interesting to note that the renal pelvis and infundibula were surrounded with adult connective tissue. Bacteria were found in one of 2 cases studied for their presence by Vest and Barelare; none were noted in our case. Whereas in peri-ureteritis plastica the fibrous envelope stripped easily from the ureter, in our case it stripped from the kidney only with difficulty. Furthermore, on microscopic examination the renal capsule was not demonstrable and fibrils of connective tissue could be seen actually extending into renal cortex.

The present case gave no history of urinary tract disease except for one episode of gonorrheal urethritis treated with sulfa drugs 15 years previously. Five years later the patient received "606 shots" for a lesion on the glans penis presumed at the time of therapy to be luetic. Serological tests at the time of hospitalization were negative. On the other hand, the patients with peri-ureteritis plastica gave past histories of urinary tract disease. Of questionable significance is the fact that all of Vest and Barelare's cases involved the right side while in ours the pathological process was present on the left.

SUMMARY

An apparently previously undescribed entity, with certain similarities to Vest and Barelare's peri-ureteritis plastica, is reported.

An extensive envelope of fibrous tissue was found around the left kidney and spleen with firm attachments to the diaphragm, tail of the pancreas and colon. The mass was of such size and density that it suggested an extensive neoplasm. It was removed *en bloc* with the regional lymph nodes.

The organs enclosed by the fibrous tissue envelope were normal. The kidney was normal except for chronic inflammatory changes in the more peripheral parts of the cortex and fibrosis around the renal pelvis and calyces.

The fibrous tissue envelope showed chronic inflammatory changes on microscopic section but no bacteria.

The pathogenesis of this process, as well as that of peri-ureteritis plastica, remains undetermined.

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PERMANENT DIVERSION OF URINARY STREAM

JOHN K DE VRIES

In December 1952, questionnaires were sent to members of the American Urological Association, in an effort to obtain a consensus in the difficult and controversial problem, permanent diversion of the urinary stream It was gratifying to receive more than three hundred and fifty replies, many with accompanying letters, giving detailed information I wish to express my very sincere appreciation to those who answered

The data compiled and analyzed show definite preferences which I will report to you in detail

Whenever the integrity of both ureters or the single ureter of a solitary kidney is compromised by trauma, stricture, tumor or neurogenic lesion and cannot or should not be repaired by classical methods, whenever the bladder must be sacrificed and whenever otherwise incurable urinary incontinence exists, permanent diversion of the urinary tract must be considered Certainly whenever feasible, the integrity of the urinary tract must be preserved The principle of intubated ureterostomy, as advocated by Davis,[1] and the use of ileal segments as substitute ureters, as used by Rack,[2] may save some patients from permanent diversion of the urinary stream when a long segment of ureter is strictured or destroyed It is possible that the use of ileal or colon grafts to enlarge contracted bladders may save other patients from permanent diversion However, in cases of cystectomy unless or until new bladders can be fashioned complete with a satisfactory sphincter mechanism, urinary diversion will be necessary (Possibly Kinman et al [3] and Lowsley et al [4] have attained this)

The choice of whether to divert the urinary stream internally or externally must then be considered This choice lies mainly between ureterosigmoidostomy on the one hand and on the other hand ureterocutaneous ureterostomy, ureterostomy in situ, pyelostomy and nephrostomy Transplantation of the ureters to an isolated loop of intestine lies in an intermediate position Any choice has objectionable features The hazards of ureterosigmoidostomy are hyperchloremic acidosis, leakage at the site of implantation, peritonitis, adynamic ileus, stricture and pyelonephritis Attesting to the unsatisfactory status of this procedure are the numerous attempts being made to modify it A few of the recent attempts are illustrative Nesbit[5] and Cordonnier[6] used mucosa to mucosa techniques to insure an open lumen This discourages stricture but invites ascending infection Willy Mathisen[7] has devised an ingenious nipple to improve the valve action Roger

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[3] Kinman, I M Arch Surg 66 531–537 1953
[4] Lowsley O Johnson T H and Rueda A E J Internat Col Surg , 20 457–462, 1953
[5] Nesbit R M J Urol , 61 · 728 1949
[6] Cordonnier J J J Urol 63 276, 1950
[7] Mathisen, W Surg , Gynec & Obst , 96 · 255 258, 1953

Baker et al.[8] have suggested cortisone to inhibit stricture formation at the anastomatic site. Others in an attempt to eliminate secondary infection from bowel contaminants have transplanted the ureters into isolated loops of colon or ileum. However, even when ureterosigmoidostomy is apparently successful, the patient may suffer from hyperchloremic acidosis; and whether his symptoms are produced solely by re-absorption, as thought by Mitchell and Valk,[9] or by absorption plus renal impairment, as thought by Lapides,[10] his lot is not a happy one. The advocated treatment: low sodium diet plus forcing fluids 4–5,000 cc daily, plus sodium bicarbonate plus frequent bowel evacuation every one to two hours, might seem a higher price to pay than the nuisances of external drainage.

External drainage may be considered as follows:

URETEROCUTANEOUS URETEROSTOMY

This technically easy and relatively safe procedure totally diverts the urinary stream. Large, thick-walled ureters, less likely to be satisfactorily transplanted into the bowel, lend themselves readily to skin transplantation and are in fact the most suitable. The operation is applicable whether the renal pelvis be intra- or extrarenal. If intubation in necessary the position of the ureterostomy is easily accessible and tubes can be re-inserted without difficulty. No electrolytic imbalance ensues.

But cutaneous ureterostomies, particularly when small, thin-walled ureters are transplanted, are prone to be involved by peri-ureteritis and stricture formation both at the ureterostomy sites and where ureter traverses fascia. This has not been solved in my hands by pedicle grafts. Care is necessary to prevent angulation and, if intubated as is frequently necessary, a long expanse of catheter is in contact with ureteral mucosa. Polyethylene and polyvinyl tubing are less likely to become encrusted than rubber tubing, but their inflexibility causes discomfort to the wearer. Fagerstrom has suggested the importance of marking the site of the proposed stoma indelibly with the patient in the standing position and bringing the ureter out to this point at operation.

This operation is obviously unsuitable for high ureteral obstruction.

URETEROSTOMY IN SITU

This procedure, according to Vose and Dixey,[11] has several advantages over nephrostomy or ureterocutaneous anastomosis such as minimal surgery, lack of renal insult, the opening may be made as high in the ureter as necessary, tubes are well tolerated and easily changed and no strictures develop.

We have used ureterostomy in situ on two occasions. In the first (K. H., No. 43950 O.M.H.) a woman weighing 400 pounds with a calculus in the midureter completely blocking the left kidney, was drained by this method for 2 weeks following stone removal. Restoration of kidney function was complete.

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[8] Baker, R., Govan, D., Huffer, J. and Cason, J.: J. Urol., **70:** 58–67, 1953.

[9] Mitchell, A. D. and Valk, W. L.: J. Urol., **69:** 82–95, 1953.

[10] Lapides, J.: Surg., Gynec. & Obst., **93:** 691, 1951.

[11] Vose, S. N. and Dixey, G. M.: J. Urol., **69:** 503–506, 1953.

In the second case, Mrs W, No 76307 O M H, right ureterostomy in situ was done because of obstruction from cervical carcinoma Tube replacement was unsuccessful and secondary nephrectomy was done

PYELOSTOMY AND NEPHROSTOMY

Pyelostomy and nephrostomy drainage may well be discussed together In common, they both are capable of diverting the urinary stream at a high level Pyelostomy obviates traversing the renal cortex, but it is necessary to mobilize the kidney to adequately expose the pelvis If the pelvis is intrarenal, pyelostomy is impossible or inadvisable The course of a pyelostomy tube is indirect and devious

Nephrostomy is ideally suited to large hydronephrotic kidneys in which the cortex is thin Here, without mobilizing the kidney, a trocar may easily be inserted and, through it a whistle tipped drainage tube This method is safe, quick and sure It carries few if any, complications

If the renal cortex is not thinned, it becomes hazardous to attempt to reach the pelvis blindly In such cases it is wiser to expose the pelvis, pass a Kimball[19] hook outward, preferably through the inferior calyx and bring the nephrostomy tube fitting snugly downward until it reaches its proper position in the pelvis If the lower pole of the kidney is brought up to the abdominal wall and sutured to it, the nephrostomy tube may be fixed anteriorly It is important to check the position of the nephrostomy tube with pyelography and, when perfect position has been obtained, the distance to the skin should be accurately measured The tendency is to push tubes in too far Tubes should be left in place four to six weeks postoperatively before changing, to form a good sinus tract

In an effort to find out how urologists the country over were diverting the urinary stream the following question was asked

> What method do you prefer in effecting permanent diversion of the urinary stream when indicated in such cases as the following?
>
> 1) Bilateral hydronephrosis and hydro-ureter in spina bifida
> 2) Inoperable carcinoma of bladder with ureteral obstruction
> 3) Urinary incontinence due to tuberculous cystitis with solitary acquired kidney
> 4) Inoperable ureteral obstruction in single kidney

Methods of diversion

Ureterosigmoidostomy
Ureterocutaneous transplantation
Ureterostomy
Pyelostomy
Nephrostomy

The answers to this question were first tabulated in general to find out whether external or internal forms of diversion were preferred The results are as follows

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[19] Kimball, F N J Urol, 44 1, 1940

External		
Nephrostomy	35 per cent	72 per cent
Ureterocutaneous	33 per cent	
Ureterostomy	1 per cent	
Pyelostomy	1 per cent	
Internal—Ureterosigmoidostomy		28 per cent

Answers were then considered in relation to the specific indications.

DIVERSION IN BILATERAL HYDRONEPHROSIS AND HYDRO-URETER IN SPINA BIFIDA

The following cases may be considered as examples:

R. M. L., No. 68985 Overlook Hospital, Summit. A 7-year old girl was admitted April 30, 1951 complaining of urinary incontinence and backache. She had been born with a meningocele for which she had had an operation when one month old. Since this time there had been difficulty in defecation and urinary incontinence. The urine was grossly infected and azotemia was present. Urea nitrogen 83 mg. per cent. Cystograms showed bilateral reflux with marked hydronephrosis and hydro-ureter (fig. 1). Bilateral nephrostomies, May 2, 1951. There was immediate and maintained improvement. On May 12 the urea nitrogen had dropped to 51 mg. per cent. Drainage is maintained with rubber whistle tipped catheters which are irrigated daily and changed every 2 weeks.

Preferences for the type of drainage received from the questionnaire were as follows: Nephrostomy, 48 per cent; ureterosigmoidostomy, 23 per cent; ureterocutaneous, 14 per cent; cystostomy, 10 per cent; pyelostomy, 4 per cent and ureterostomy, 1 per cent.

DIVERSION IN INOPERABLE BLADDER CARCINOMA WITH URETERAL OBSTRUCTION

Preferences for the type of drainage received from the questionnaire were as follows: ureterosigmoidostomy, 51 per cent; ureterocutaneous, 27 per cent;

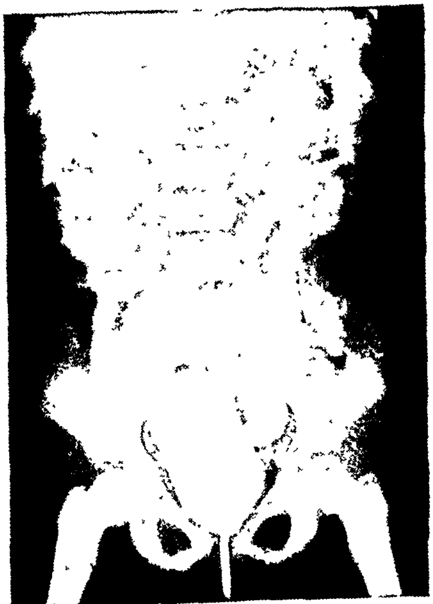

FIG. 1. R. M. L., No. 68985, O. V. Spina bifida. Cystogram discloses bilateral reflux, bilateral hydronephrosis and hydro-ureter.

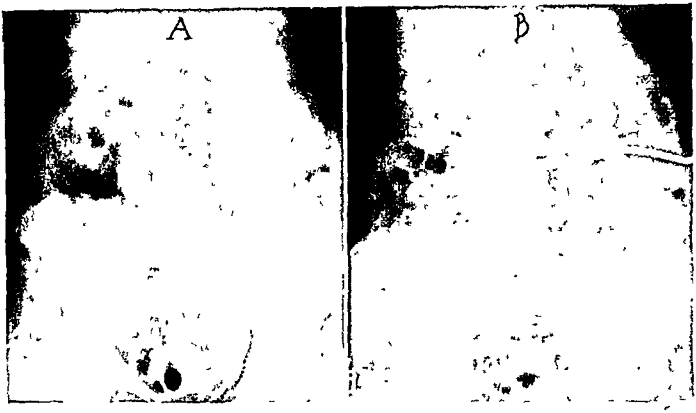

FIG. 2 D. N., No. 282665, O. M. H. Inoperable carcinoma of bladder. *A*, dilatation of lower ureter of only functioning kidney. *B*, excretory urogram following ureterosigmoidostomy.

nephrostomy, 14 per cent; no surgery, 5 per cent; pyelostomy, 2 per cent; ureterostomy, 1 per cent.

In inoperable bladder carcinoma with ureteral obstruction 5 per cent advised no surgery and argue "why prolong suffering needlessly?" Why not an immediate uremic death rather than a prolonged death from carcinomatosis? This argument merits consideration. However, when severe frequency and dysuria are present, diversion of the urinary stream may be justified by the relief of these symptoms.

The following case is illustrative (fig. 2). D. N., No. 282665 O.M.H., was seen in 1939 at age of 55 when suprapubic cystotomy and radon implantation were done for epidermoid carcinoma grade 2 involving the bladder neck. During the next 10 years several transurethral fulgurations were done and the urethra required dilatation at regular intervals. By 1949 the right kidney had become functionless and there was marked dilatation of the lower left ureter. Left ureterosigmoidostomy, Nesbit type, was done at this time, but in spite of an apparently successful transplant, hyperchloremic acidosis developed. Left nephrostomy was done 2 months later and from this time until death occurred after 2½ years the patient was quite comfortable and renal function remained satisfactory in spite of tremendous tumor growth which eventually produced intestinal obstruction.

DIVERSION IN URINARY INCONTINENCE DUE TO TUBERCULOUS CYSTITIS WITH SOLITARY ACQUIRED KIDNEY

Here the preference according to the questionnaire was ureterocutaneous transplantation, 47 per cent; nephrostomy, 26 per cent; ureterosigmoidostomy, 20 per cent; pyelostomy, 4 per cent; ureterostomy, 3 per cent Ureters in these cases are usually thick-walled and lend themselves well to skin transplants. However, many cases have been successfully transplanted into the bowel.

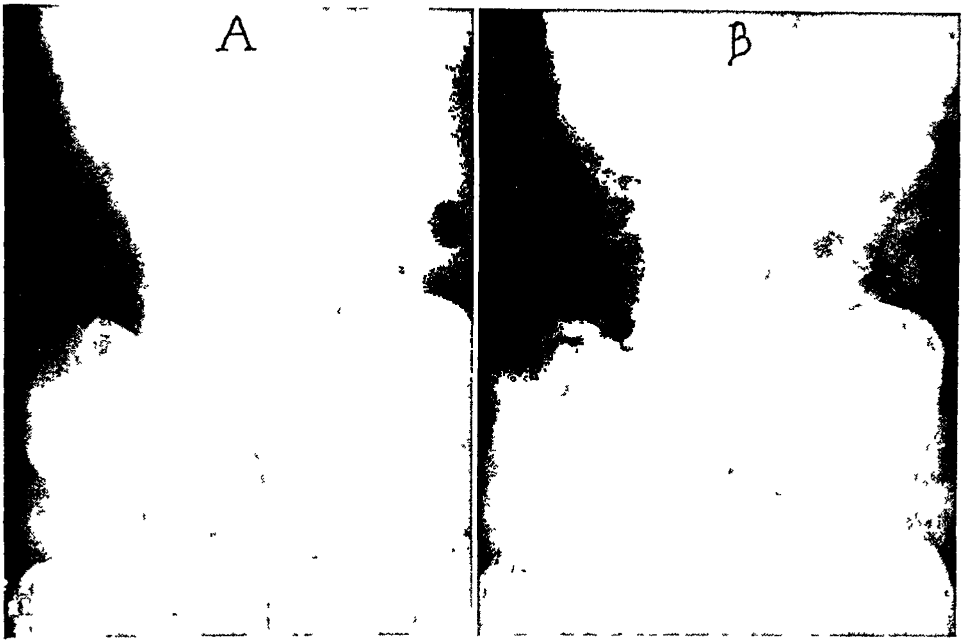

FIG 3. L., No. 50106, O. M. H. Tuberculous cystitis; incontinence. *A*, obstruction of ureter in solitary kidney. *B*, nephrostomy.

In the following case, nephrostomy seemed to be the answer to a particular problem. Mrs. M. L., aged 72, No. 50106 O.M.H., had had a right nephrectomy at the age of 45 for tuberculosis. At the age of 58 she suffered from complete urinary incontinence due to a chronically contracted bladder. Bladder calculi were removed at age of 62 and again at age of 64. At 68 anuria developed due to obstruction at the ureteropelvic junction. Emergency nephrostomy proved effective and so relieved urinary incontinence that it has been maintained as permanent drainage. See figure 3.

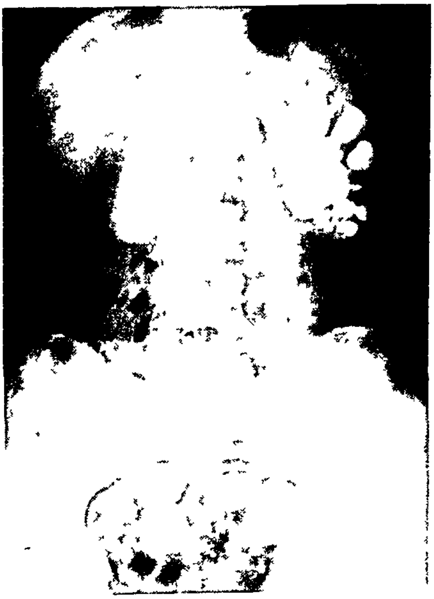

FIG. 4 D. G., No. 189620, O M. H Nephrostomy for ureteral obstruction in solitary acquired kidney.

DIVERSION IN INOPERABLE URETERAL OBSTRUCTION IN SINGLE KIDNEYS

The following cases may be cited as examples

D G , No 189620 O M H , a man aged 45, had undergone right nephrectomy for hydronephrosis at age of 20 At 28, obstruction at the ureteropelvic junction on the left was treated by nephropexy and pyelotomy The ureteropelvic junction was examined at this time and dilated to 14F The obstruction was unimproved by the operation and within a few months left nephrostomy was done At this time the lower calyx was traumatized and required suture because of hemorrhage The nephrostomy tube was then placed in the middle calyx This nephrostomy has been successfully maintained for 18 years See figure 4 The patient wants no further surgery and I have no desire to urge him otherwise

Preferences for the type of drainage received from the questionnaire for this type of case were as follows nephrostomy, 63 per cent, ureterocutaneous, 19 per cent, pyelostomy, 9 per cent, ureterostomy, 6 per cent, ureterosigmoidostomy, 3 per cent *

REPLIES TO QUESTIONNAIRE

Because I have long been interested in the subject of permanent nephrostomy and its place as a method of diverting the urinary stream the following question and answers are reported

How many cases of permanent nephrostomy do you have in your practice?

28 per cent indicated 0
66 per cent indicated under 10
6 per cent indicated over 10

How long have you been able to maintain drainage satisfactorily?

Less than 5 years	48 per cent
5 9 years	32 per cent
Over 10 years	20 per cent

What complications have occurred with nephrostomy drainage?

Immediate		*Late*	
Hemorrhage	24 per cent	Calculus formation	43 per cent
Infection	59 per cent	Poor drainage	28 per cent
Loss of kidney	11 per cent	Inability to replace tube	28 per cent
Death	6 per cent	Other causes	1 per cent
Other causes			

What type of tubing do you use for nephrostomy?

dePezzer, wing, whistle tip, rubber, polyethylene—

---

* Probably considered for lower ureteral obstruction

The answer to this question is tabulated as follows:

	In general	49 urologists who maintained satisfactory drainage for over 10 years
Rubber	36 per cent	40 per cent
Polyethylene	15 per cent	10 per cent
Whistle tip	17 per cent	21 per cent
Wing tip	17 per cent	11 per cent
dePezzer	15 per cent	18 per cent

At what intervals do you change nephrostomy tubes?

	In general	49 urologists who maintained satisfactory drainage for over 10 years
Monthly	37 per cent	47 per cent
Longer intervals	29 per cent	23 per cent
Bimonthly	16 per cent	12 per cent
As needed	12 per cent	12 per cent
Weekly	6 per cent	6 per cent

At what intervals do you advise irrigation of nephrostomy?

	In general	49 urologists who maintained satisfactory drainage for over 10 years)
Daily	46 per cent	68 per cent
Twice daily	20 per cent	12 per cent
Longer intervals	20 per cent	14 per cent
None	11 per cent	6 per cent

What contra-indication do you find to nephrostomy drainage?

35 per cent found no contra-indication.
Contra-indication as reported in the order of frequency was as follows:

Too difficult for patient	51
Patients dislike	24
Nuisance to patient and physician	18
Stone formation	17
Small renal pelvis	13
Good as emergency measure	13
Odor	11
Infection	9
Leakage around tubes	5
Tuberculous kidney	2

CONCLUSIONS DRAWN FROM QUESTIONNAIRE

There is no ideal method of permanent diversion of the urinary stream.

Weight of opinion, as evidenced by questionnaire, shows 72 per cent to 28 per cent in favor of external diversion; that external forms of drainage nephrostomy and ureterocutaneous anastomosis are equally popular; that ureterostomy and pyelostomy are rarely used.

Nephrostomy was the operation of choice in bilateral hydronephrosis and hydro-ureter due to spina bifida and in inoperable ureteral obstruction in single kidneys. Ureterocutaneous transplantation was the operation of choice in urinary incontinence due to tuberculous cystitis with solitary acquired kidney Ureterosigmoidostomy was the operation of choice in inoperable bladder carcinoma with ureteral obstruction

Twenty-eight per cent of the urologists indicated that they had not performed nephrostomy, 66 per cent had done less than 10, and 6 per cent, more than 10

While it is possible to maintain nephrostomy drainage indefinitely, 48 per cent of the urologists indicated a span of less than 5 years, 32 per cent between 5 and 9 years, 20 per cent over 10 years

The most important complications reported with nephrostomy drainage were infection (early) and calculus formation (late)

Nephrostomy drainage is a satisfactory form of diversion where urologist and patient co operate to maintain meticulous after-care

129 Summit Ave, Summit, N. J.

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URETERAL OBSTRUCTION IN THE AGLOMERULAR KIDNEY

STANWOOD S. SCHMIDT

The study of hydronephrosis has been limited in the past to research on the glomerular kidney. It has been assumed that a glomerulus was essential for the development of hydronephrosis, but proof of this has been lacking. The following experiment shows that hydronephrosis does not develop in an aglomerular kidney following ligation of the ureter.

Hydronephrosis has been defined by Hinman (1934) as "the term applied to the renal changes of pelvic dilatation and parenchymal atrophy, with urinary obstruction." These changes have been studied in many animals with glomerular kidneys. They occur in apelvic kidneys as well as in those possessing a pelvis. This phenomenon is not limited to mammalian kidneys. It may occur in the kidneys of glomerular fish.

Hinman has further stated that a continued secretion of urine takes place in spite of obstruction up to the point of complete tissue destruction. He has shown that the degeneration is produced by a combination of both pressure and anemia.

In hydronephrosis, tubular degeneration occurs as a relatively early process and the glomeruli are among the last to atrophy. It has thus been assumed that the glomerulus is essential for the development of hydronephrosis.

Hinman has stated that an aglomerular kidney would not show the changes characteristic of hydronephrosis following ureteral obstruction. He has assumed that it would develop a primary atrophy and that destruction of this kidney would occur from primary atrophy.

Since it is impossible to eliminate the glomeruli from a kidney in order to study the behavior of the tubules alone following ureteral obstruction, the existence of a purely tubular kidney offers an opportunity for the study of a kidney in which the glomeruli have been eliminated by evolution. Such a kidney is to be found in the midshipman fish, Porichthys notatus. Ureteral ligation was carried out in this fish and the results studied. See figure 1.

MATERIALS AND METHODS

The most widely known group of vertebrates which possesses an aglomerular kidney consists of certain teleosts, or true fishes, of which the toadfish of the Atlantic Coast is the best known. The seahorse and the pipefish also belong to this group.

Several years ago it was learned that the midshipman (Porichthys notatus), a fish common on the Pacific Coast, possesses an aglomerular kidney. This fish is about a foot long, was easily obtained, is very hardy, and thus made an ideal experimental subject.

At the onset of the experiment, serial sections were made of the kidneys of

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Read at annual meeting, Western Section of American Urological Association, Victoria, B. C. April 19–22, 1954.

Note by editor. Dr. Schmidt's paper was awarded the Joseph F. McCarthy Prize Essay Competition sponsored annually by the Western Section.

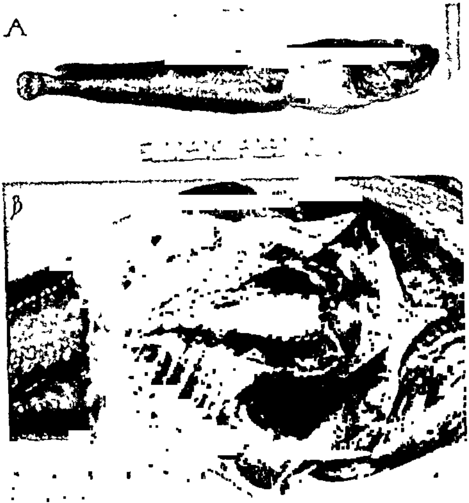

Fig 1 *A*, midshipman fish, Porichthys notatus. *B*, view of midshipman with abdomen dissected to show kidneys and ureters.

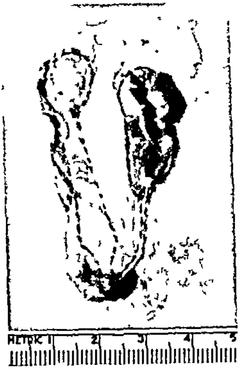

Fig. 2 Kidneys and ureters 12 days following ligation of ureter of kidney on left

both immature (3 cm.) and adult fish. These revealed that the kidney was entirely aglomerular in both and revealed no evidence of an arterial blood supply to the kidney.

The aglomerular kidney consists of tubules, surrounded by the abundant lymphatic tissue characteristic of all fish kidneys. It lacks an arterial blood supply and is supplied entirely by a renal portal system. The nephron consists of a proximal convoluted segment, lined by one cell type, and an initial collecting

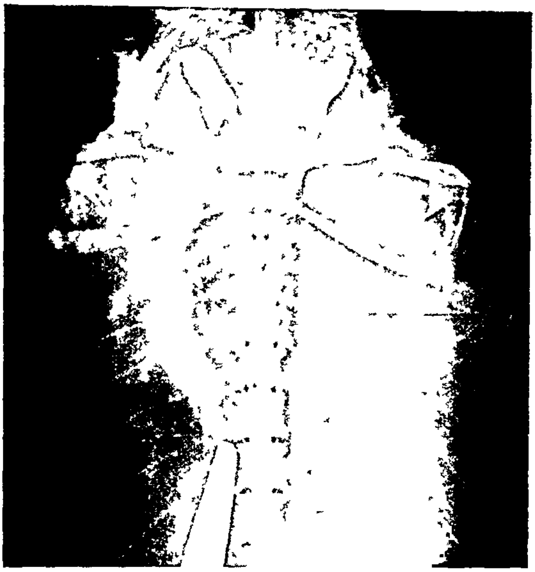

FIG. 3. Retrograde pyelogram after 12 days of obstruction Tip of Kelly clamp is shown.

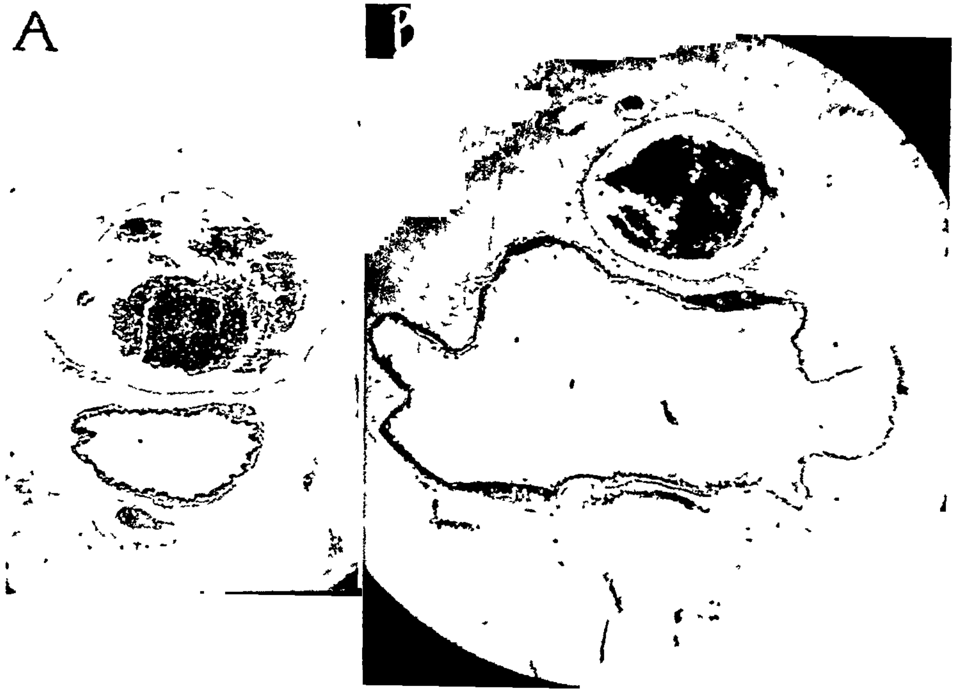

FIG. 4. Photomicrographs of ureter and portal vein of normal, *A*, and 12 day postoperative, *B*, specimens. Vein is above.

segment. A large collecting duct within the kidney becomes a distinct ureter between the kidney and the bladder and is accessible surgically. The distal convoluted tubule is regularly absent in all marine fishes, while most fish have a long ribbon-like kidney without a distinct extrarenal ureter.

The fish were kept in large salt-water tanks. Inasmuch as the fish would not eat in the aquarium, it was seldom possible to keep them alive, even unoperated,

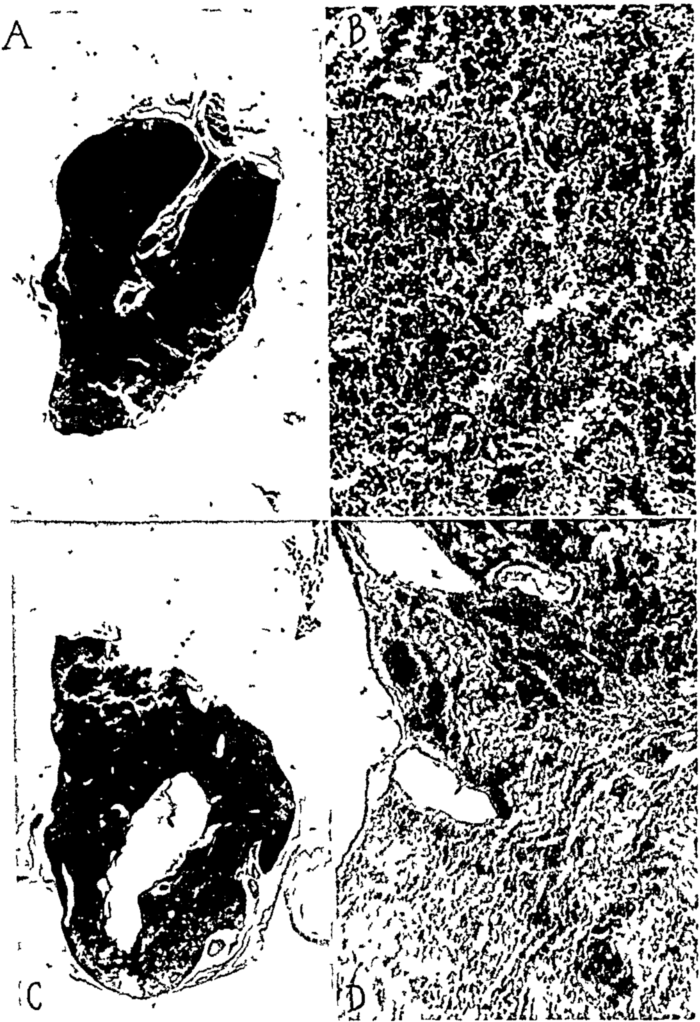

Fig 5 *A* and *B*, cross sections, normal kidney *C* and *D*, cross sections after 12 days of obstruction Dilatation of collecting ducts is seen Secretory tubules are unchanged throughout

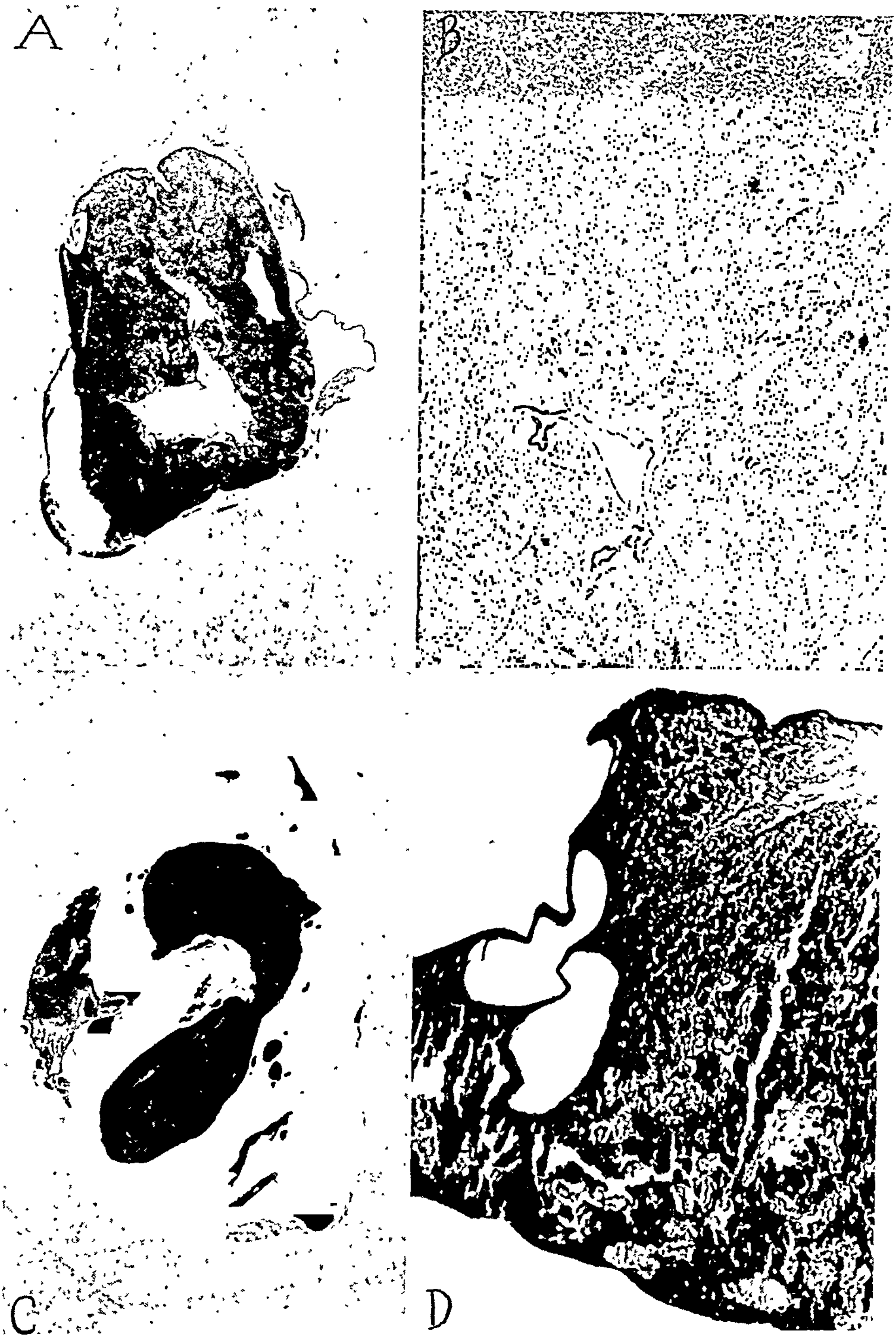

FIG. 6. *A* and *B*, cross section after 49 days of obstruction. *C* and *D*, cross sections after 108 days of obstruction. Dilatation of collecting ducts is seen. Secretory tubules are unchanged throughout.

longer than four months and it was considered remarkable if one of the fish passed the hundredth postoperative day

The fish were anesthetized by placing them in sea water in which "M S 222" (Sandoz) had been dissolved in a strength of 1:3000 This drug proved very safe and allowed the fish to recover within a minute of returning them to pure sea water

The ureter was approached transabdominally It was freed from its intimate approximation to the renal portal vein, doubly ligated with cotton, and divided Closure was made in layers with interrupted cotton sutures The use of sterile technique was impractical inasmuch as any sort of antiseptics would have severely damaged the skin Wound disruption, renal infection and infection of the abdominal cavity were common and proved a major complication

OBSERVATIONS

The results of these experiments are graphically shown in figures 2 to 6, which conclusively demonstrate that a marked dilatation of the ureter and of the major collecting ducts within the kidney proper occurs and progresses The epithelium of these ducts is changed with dilatation from a high columnar to a low cuboidal and finally to a squamous type No changes can be noted in the epithelium of the secretory tubules at any stage following obstruction, and even in the most advanced case these secretory cells appear no different from those in the nonobstructed kidney There is no evidence of dilatation of the secretory tubules themselves There is no evidence of atrophy, either primary or hydronephrotic No gross evidence of compensatory hypertrophy was seen

Definite changes are to be noted in a comparison of cross sections of the kidney after different periods of obstruction These are most marked between the normal and the 12-day specimen and between the 12 day and the 43-day specimen Little evidence of progression is seen between the 13-day and the 108-day specimen In the latter the secretory tubules are normal in appearance and the changes are confined to the ureter and collecting ducts Similar changes were found in all preparations studied See figures 5 and 6

DISCUSSION

All aglomerular fish live in salt water This seems peculiar until one considers several additional facts The first of these is that the aglomerular kidney secretes an extremely small amount of urine Secondly, up to 90 per cent of the water absorbed by the gut of the marine fish may be eliminated extrarenally The resulting small volume of urine is linked with the absence of glomeruli

Along with the extrarenal elimination of water, there are additional mechanisms of excretion open to the marine fish Sodium, potassium, chloride, and water are excreted by the gills, while the kidney excretes calcium, magnesium, sulfate, phosphate and nitrogen It is seen that the kidney of the marine fish cannot perform all of the functions of the mammalian kidney

It is to the advantage of any marine fish to be able to secrete a concentrated urine of low volume. The aglomerular kidney is able to secrete a more concentrated urine than is the glomerular kidney. A marine fish with a glomerular kidney must perform a great amount of uneconomical work against the high osmotic force of sea water in order to obtain sufficient fluid to carry its wastes away.

Hydronephrosis has its most typical expression in the (mammalian) kidney which has a pelvis. It has been shown that a pelvis is unnecessary for its development and that hydronephrosis occurs in the apelvic kidneys of reptiles, birds and amphibia and in the glomerular apelvic kidney of the fresh water catfish.

The atrophy of hydronephrosis is a result of backpressure and of the anemia secondary to this backpressure. The excretory pressure of all glomerular kidneys is below arterial blood pressure. In spite of its venous blood supply, the secretion pressure of the aglomerular kidney may exceed the aortic blood pressure. In the mammalian salivary gland and pancreas, which have an arterial supply, the secretion pressure likewise may exceed arterial blood pressure.

The balance which permits the development of hydronephrotic atrophy in the apelvic kidney is that between excretion and tubulo-venous backflow. Hinman has stated that other glands fail to show this balance and so develop primary atrophy upon obstruction of their ducts.

Primary atrophy, in contrast to hydronephrotic atrophy, has been defined as a type of tubular degeneration without dilatation which follows the complete obstruction of the excretory duct of glands other than the kidney. MacCallum, in 1909, demonstrated this to occur in the pancreas following ligation of the duct draining a portion of the gland. Hinman has stated that primary renal atrophy is seen only following anuria. Proof of this, demonstration of the mechanism of the production of the predisposing anuria, and demonstration of the exact type of anuria, is lacking.

The changes after obstruction of the ureter of the aglomerular kidney represent neither hydronephrosis and hydronephrotic atrophy nor primary atrophy, since at no stage in the experiment was atrophy noted. Some of the features of hydronephrosis were present: obstruction, increased intrarenal pressure and dilatation of the collecting ducts and ureter. The condition of the secretory epithelium argues that no interference with the blood supply occurs, even though this supply is purely venous. It is doubtful that the low urine volume normally present is a significant factor, since the process of hydronephrosis develops regardless of urinary volume. The dilatation of the collecting ducts shows that secretion occurs after obstruction, yet no dilatation of the secretory tubules occurs. Any conclusions which can be drawn on the basis of these results point to either a condition of balance between secretion and absorption, or to a cessation of secretion without atrophy.

This work raises serious questions regarding the validity of previous concepts. Complete re-evaluation of the mechanism of primary atrophy is in order. Most of the work dealing with this has been done in glands which secrete enzymes which may cause autolysis. The considerable interstitial fibrosis seen in the obstructed pancreas has been found to be caused by this leakage of enzymes.

The well known sebaceous cyst is an excellent example of obstruction of a nonenzymatic gland. This occurs without atrophy and without loss of the power to resume secretion. I believe that the behavior of this gland is more closely comparable to that of the aglomerular kidney than is the behavior of an enzymatic gland. It is postulated that a cessation of activity eventually occurs in the aglomerular kidney. Since the secretory cells of the obstructed aglomerular kidney are microscopically indistinguishable from the actively secreting cells in the control kidney, it is to be expected that this kidney could resume its function upon removal of the obstruction and would never atrophy.

SUMMARY AND CONCLUSIONS

Following complete obstruction of the ureter of the aglomerular kidney of the midshipman fish, pronounced dilatation of the ureter and intrarenal collecting ducts occurs, progressing to a point microscopically indistinguishable from that occurring in hydronephrosis

There is no evidence of dilatation or atrophy of the secretory tubules following this obstruction. This lack of atrophy may be explained by postulating that a cessation of function occurs and that the venous blood supply to the kidney is adequate in spite of increased tubular pressure.

The presence of glomeruli is not essential to the development of a marked degree of dilatation of the ureter and collecting ducts, comparable to that seen in hydronephrosis The lack of dilatation and atrophy of the secretory tubules shows that neither hydronephrosis nor primary atrophy occurs following obstruction of the aglomerular kidney.

The presence of glomeruli seems essential to the development of hydronephrosis.

This experiment was carried out while the author was a member of the Division of Urology of the University of California Medical School.

The encouragement given by Dr. Frank Hinman, Jr. is gratefully acknowledged. The facilities of the Steinhart Aquarium of the California Academy of Sciences were graciously extended and proved essential to this work. The fish were secured through the kindness of the A. Paladini Fish Co.

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URETERAL ECTOPIA AS A CAUSE OF CHRONIC INFECTION

JAMES F. O'MALLEY AND JAMES E. BUMGARNER

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Ureteral ectopia, wherein the ureter opens into the seminal vesicle, has been reported in the literature 40 times. Of this number, only 8 have been diagnosed clinically, the remainder having been cited as autopsy findings. Most of the cases reported showed some congenital abnormality or absence of the kidney on the same side. The left side was affected more often than the right, a fact which has not been explained.

Urinary tract infection was the presenting complaint in all clinically diagnosed cases except the last three. Of the latter, Engel's patient first consulted his physician regarding sterility; and the ureteral ectopia was considered the cause. Meisel's patient complained of rectal discomfort; Hamilton, et al. reported it as an additional finding subsequent to trauma.

The embryological explanation has been completely reviewed by Riba et al., and will be briefly presented. The explanation lies in the failure of the ureteral buds to shift upward to assume their normal opening in the trigone. Because of the close relationship of the wolffian derivatives (posterior urethra, vas deferens, epididymis and seminal vesicles) and the ureteral buds, an ectopic opening into any of these structures can occur.

The present case is of interest not only as an addition to the literature, but also because of the long interval before complete urological study in the presence of recurrent infection was done. This congenital abnormality should be considered in the search for an obscure source of pyuria; and the necessity for careful search for the cause of recurrent urinary infection should be re-emphasized.

CASE REPORT

C. L. (R 138), a 27 year old white married man, entered the V. A. Hospital, Kansas City, Mo. October 12, 1952, complaining of terminal hematuria and hematospermia of 2 weeks' duration. In 1944, following gonorrheal urethritis, recurrent acute epididymitis developed and necessitated frequent treatment until 1946, at which time a left epididymectomy was done. He continued to have intermittent backache and left testalgia. The dull ache in the testicle seemed to extend along the inner aspect of the left thigh. About two weeks before this admission, he noticed mild irritative urinary symptoms and terminal hematuria in the form of stringy clots. Two episodes of hematospermia occurred about the same period. The patient had been married 4 years and had noted no abnormality of sexual activity. He had two children. The remainder of the past and family history was noncontributory. The physical examination was negative except for a slightly enlarged left testicle and an indurated remnant of the upper pole of the left epididymis.

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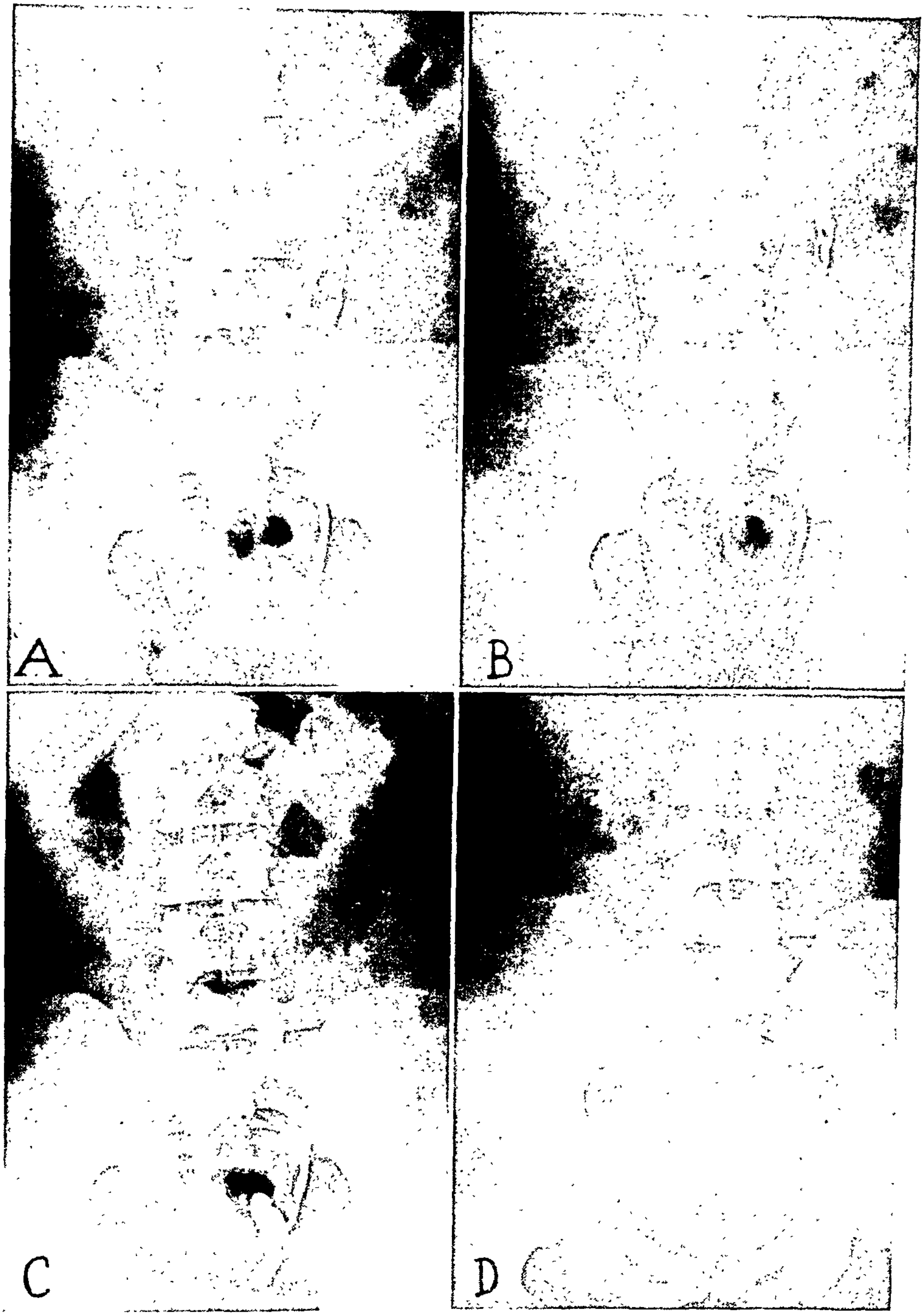

FIG. 1. *A*, retrograde pyelogram demonstrating relation of ureter and left seminal vesicle. *B*, normal right pyelogram and hypoplastic left kidney. *C*, drainage film following retrograde pyelogram. *D*, injection of scrotal vas deferens.

Routine examination of the blood was negative The urine showed 6 to 8 white blood cells per high powered field Urine culture resulted in a heavy growth of hemolytic staphylococcus

At cystoscopy, an absence of the left half of the trigone was noted, and the left ureteral orifice was seen as a patulous linear opening just inside the vesical neck at 5 o'clock Retrograde pyelograms (fig 1, *A* and *B*) revealed a left hypoplastic kidney with a normal sized ureter emptying into the left seminal vesicle Thus the seminal vesicle acts as the terminal ureter Excretory pyelography revealed excellent function bilaterally, again filling the seminal vesicle

Because of the normal function of the left kidney and no history of renal infection, it was believed that the ureter and kidney were best left alone Accordingly, surgery was confined to a left vasectomy to prevent further reflux of urine to the epididymal remnant Injection of the vas as suggested by Meisel was done at the time of vasectomy (fig 1, *D*) to further demonstrate the anomaly The patient was asymptomatic when discharged from the hospital

DISCUSSION

The only symptoms resulting from the anomaly in this case were recurrent epididymitis and seminal vesiculitis Ligation of the vas has cleared the symptoms within the scrotum Needless sacrifice of a functioning kidney or re-implantation of the ureter with the associated reflux does not seem justified at the present time Appropriate antibiotics completely relieved all vesicular symptoms and the patient has continued to remain asymptomatic for the three months since discharge

In view of the increasing number of cases diagnosed clinically, this anomaly is probably present more often than previously realized Similar causes of infection will be more readily found if this is kept in mind

It is interesting that infertility was no problem in this case

SUMMARY

The ninth case of an ectopic ureter opening into the seminal vesicle diagnosed clinically and the fortieth case reported has been presented and shown to be a cause of chronic epididymitis and seminal vesiculitis

The associated lesion was a hypoplastic kidney on the same side without symptoms

Relief of symptoms was obtained by chemotherapy and vas ligation of the affected side

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DISEASES OF URETERAL STUMP

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Recognition of existing disease in the ureteral stump subsequent to nephrectomy is not recent. However, it is felt of sufficient clinical importance to invite the attention of urologists.

The anatomical and physiologic fate of the ureter is adequately reviewed by Latchem's experimental work on the ureteral stump in nephrectomized dogs reported in 1922, with the following pertinent observations. After nephrectomy in the normal ureter there is noticeable atrophy of the muscular coat, but no attempt is made toward obliteration of the lumen by disappearance or atrophy of the mucous membrane. The same conclusion applies to the hypertrophic, hydro- or pyo-ureter when there is free drainage of the stump. However, in the obstructed ureter, the mucous membrane remains intact and the muscular coats remain hypertrophic. This latter observation has recently been amplified by Baker and Huffer in 1953 by their studies on ureteral electromyography. They recorded increased ureteral contraction in severed ureters where obstruction and hypertrophy were present. This study implies that hypertrophy is due to the work of peristalsis and, therefore, the ureteral stump is subject to the same physiologic activity as the intact ureter, capable of peristalsis, hyperperistalsis and ureteral colic.

The incidence of disease in the ureteral stump is not accurately known. Fowler in 1910 referred to Israel's report of 4 cases of empyema of the ureteral stump as a complication in a series of 900 nephrectomies. Rieser reporting in 1950 could find only 37 cases of pyo-ureter reported by 18 different authors in a 25-year period prior to 1950. He added 4 cases of his own. In his series, 17 were due to calculi, 12 due to stricture (stenosis), 2 from anomalies and in 6 the cause was not stated. It may be concluded from these reports that disease of the ureteral stump is rare. However, Senger, Bell, Warres and Tirman in 1947, reviewing a series of 22 nephrectomized patients undergoing routine urologic study, demonstrated pathological changes of the ureteral stump in 5 cases, 2 cases with stenosis of the ureteral orifice, two with calculus and 1 with reflux. Pyo-ureter was present in two of these cases. The incidence of 2 cases of pyo-ureter in a series of 22 with 3 cases, offering the possibility of subsequent disease, suggests the incidence may be much more common than its recognition.

Disease of the ureteral stump may develop many years after nephrectomy. Davison, in 1942, reports a case of pyo-ureter 17 years after nephrectomy, secondary to a calculus. The patient had been free of symptoms and urinary findings during the entire period. On the other hand, Hennessey in 1938 reported 2 cases of pyo-ureter, 17 and 23 years respectively, after nephrectomy and Ljunggren, in 1948, reported 1 case 18 years after nephrectomy; all three of these cases had suffered pyuria for long periods before the cause was recognized.

Read at annual meeting, Western Section of American Urological Association, Victoria, B. C. April 19–22, 1954.

By far the most common cause of infection in the ureteral stump is an obstructing lesion of the lower ureter; reflux with incompetent ureterovesical valve is a less frequent cause.

To pursue the problem of subsequent disease in the ureteral stump further, there is the possibility of serious secondary disease arising within the ureteral stump entirely unrelated to the process for which nephrectomy was done. Loef and Casella report a case of squamous cell carcinoma occurring in the ureteral stump 14 years after nephrectomy for hydronephrosis. To our knowledge this is the only recorded case to date of primary tumor arising in the ureteral stump.

Another consideration is the prevention of diseases of the ureteral stump. This resolves itself primarily into a consideration of the indications for ureterectomy at the time nephrectomy is done. A most complete treatise on this subject was made by Fagerstrom in 1939, in which he outlined indications for primary nephro-ureterectomy. Those pertinent are: 1) hydro- and pyo-ureteronephrosis, particularly where stricture or dilatation of the ureterovesical junction is present; 2) calculi in the ureter where drainage is in doubt; 3) renal and ureteral tuberculosis with ureteral stricture or gaping ureteral orifice. Rieser recommends nephro-ureterectomy whenever drainage of the ureter concerned is in doubt, as demonstrated by delay in drainage of radiographic media.

The following 4 cases are offered for your consideration:

CASE REPORTS

Case 1. E. L , a 58 year old housewife, underwent left nephrectomy in March 1938 for acute calculous pyonephrosis. The presence of a calculus in the left lower ureter was known at the time of operation but because of the patient's acute infection, ureterectomy was not considered Following nephrectomy, the patient remained clinically free of symptoms and positive urinary findings for a period of 11 years, when a constant, dull pain developed in the left lower abdomen associated with symptoms of cystitis, and E. coli pyuria. Exacerbations of the pain and bladder infection recurred despite chemotherapy. Complete urologic study revealed an obstructing calculus in the left ureteral segment (fig. 1). Catheterization of the ureteral segment could not be accomplished, but a satisfactory ureterogram was obtained by injecting the ureteral meatus through a bulb catheter. Following left ureterectomy in June 1951, the patient has remained clinically free of all symptoms and positive urinary findings.

Case 2. J. M , a 44 year old laborer, in July 1939, suffered typical left ureteral colic from a calculus in the lower left ureter. Cystoscopic manipulation of calculus resulted in rupture of the ureter. Immediate ureterolithotomy with drainage was done The ensuing 2 years were characterized by progressive hydronephrosis and recurrent acute left pyelonephritis This occurred despite frequent ureteral dilatations to 12F. Repeated x-rays taken during this interim revealed no evidence of calculus in the kidney or ureter.

In 1941, left nephrectomy was done because of ureteral stenosis and progressive hydronephrosis. The patient remained free of symptoms and positive urinary findings for 13 years In 1953, he suffered repeated episodes of severe colicy pain

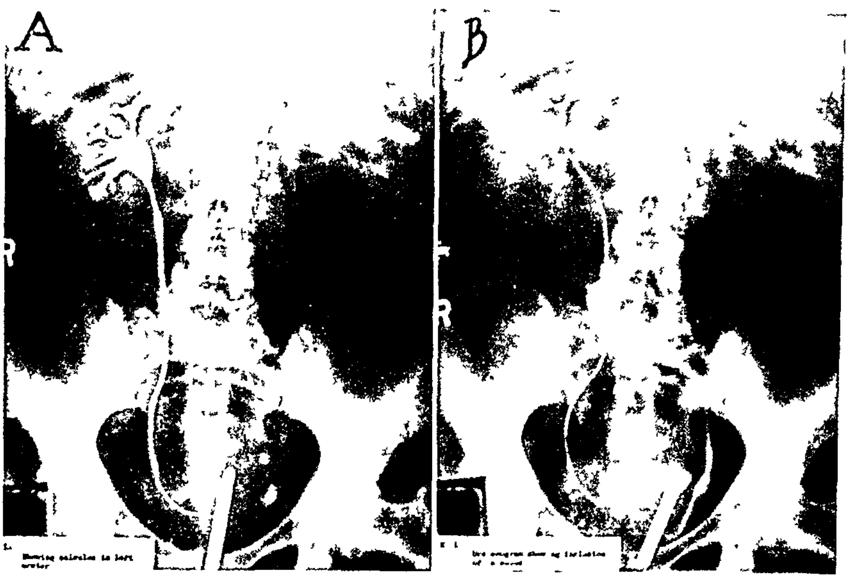

FIG. 1 *A*, right pyelogram showing calculus in region of left lower ureter *B*, left ureterogram showing calculus

in the left lower abdomen with radiation to the inguinal region and genitalia. The patient described the pain as identical to ureteral colic suffered in 1939. Urologic investigation showed a calculus in the lower left ureter with stenosis and pyo-ureter (fig. 2). Left ureterectomy and prostatectomy were done early in March 1954 with complete recovery.

Case 3. M. B., an unmarried, 47 year old office nurse, had a right nephrectomy in 1934 for renal tuberculosis. She was treated for tuberculous cystitis for 2 years following operation. No information as to associated bladder and ureteral disease is available. For the following 17 years, this patient was actively employed and asymptomatic. During October 1951 she had symptoms of acute cystitis with pyuria (B. pyocyaneus) and suppurative urethritis. Urologic study revealed brawny induration of the urethra with purulent urethral exudate, chronic cystitis with reduced bladder capacity and a gaping ureteral orifice on the right side. Excretory urograms showed a normal appearing and functioning left kidney with some left ureteral dilatation and reflux of radiopaque material into the dilated right ureteral segment (fig. 3). Smears, cultures and guinea pig inoculation were all negative for M. tuberculosis. The acute infection was controlled with difficulty by a variety of antibiotics, urethral dilatations and urethral massage. Exacerbations of urinary infection, however, recurred over the ensuing 5 months and during one exacerbation the patient suffered acute pyelonephritis. Urologic study during a remission revealed persistent infection by direct smear and culture in both the urinary bladder and the right ureteral stump. In May 1952, right ureterectomy was done following which the patient made a gradual recovery and in the past 2 years has suffered no acute exacerbations of urinary infections. She has been able to continue employment as an office nurse without interruption.

Case 4. M. G., a 43 year old male electrician, suffered acute gonorrheal urethritis in 1923, complicated by chills and fever. Urologic investigation at Johns Hopkins

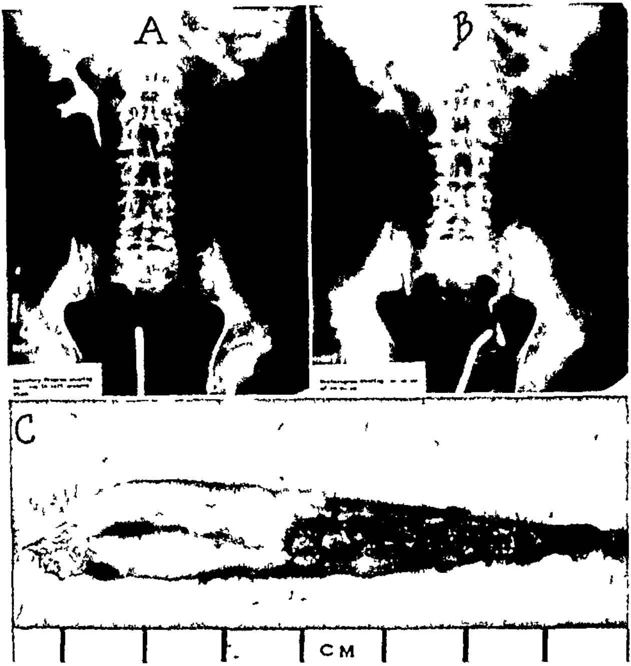

Fig 2 A, right pyelogram Calcareous density in region of lower left ureter B, left ureterogram showing stenosis with calculus above stricture C, ureteral stump opened Note calculus which developed in situ

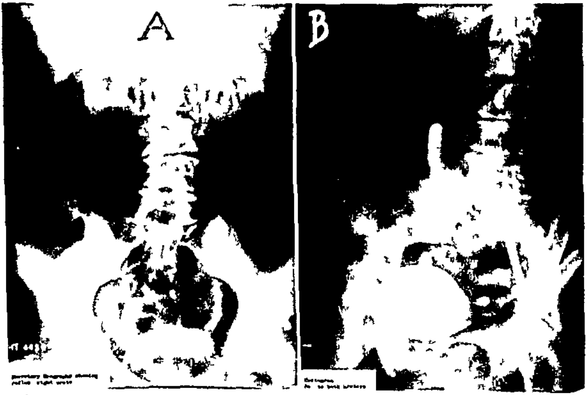

Fig 3 A, excretory urogram with reflux into right ureteral stump B, cystogram reflux into right ureteral stump

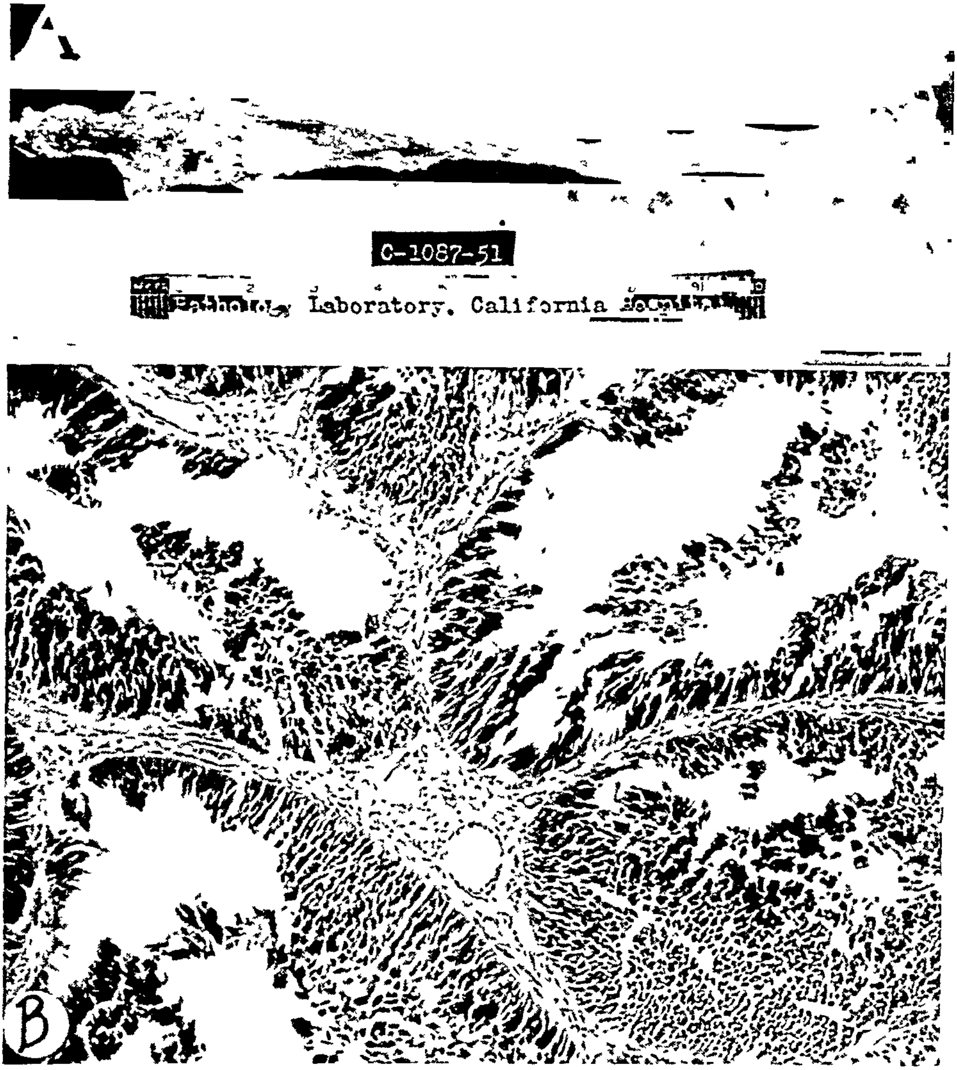

FIG 4 *A*, right ureteral stump with papillary carcinoma *B*, photomicrograph of neoplasm of right ureteral stump

Hospital revealed a large, infected hydronephrosis of the right kidney. Surgical exploration and drainage of the right kidney were instituted. Smears of the contents of the right renal pelvis revealed gonococci. Following a period of drainage, the wound healed slowly. One year later, in 1924, transperitoneal pyeloplasty was done at Johns Hopkins Hospital; this was unsuccessful and in November 1924 a right nephrectomy was done. Recovery was uneventful and the patient remained symptom-free for the ensuing 27 years.

In 1951 he suffered repeated attacks of gross total hematuria. Repeated urologic examination, including cystoscopy, revealed only low-grade prostatitis, which was considered the cause of hematuria. Cystoscopic examination in February 1951 confirmed the presence of low grade prostatitis but a bulging, prominent right ureteral orifice with a protruding papilliform mucous membrane was noted at this time. A biopsy was obtained from the protruding papillary membrane and the ureteral orifice thoroughly fulgurated. Histologic report of examination of the biopsy by Dr. Angus Wright follows: "... the specimen is made up of irregular, delicate, papillary structures covered by epithelial cells of transitional type. The epithelium shows evidence of moderate hyperplasia with occasional irregular, hyperchromatic nuclei and rare mitotic figures. The epithelium is well demarcated from the supporting connective tissue seen in the specimen. The supporting connective tissues are infiltrated with a number of small round cells. The diagnosis is papillary transitional cell carcinoma, grade 1, of right ureter" (fig. 4). A right ureterectomy was done February 18, 1951; the patient made an uneventful recovery and has suffered no attacks of hematuria since.

SUMMARY

The 4 cases presented are illustrative of disease occurring in the ureteral stump following nephrectomy.

The first 2 cases are examples of pyo-ureter secondary to obstruction from calculus and stenosis in the terminal ureter. In case 2 a calculus apparently formed in situ after nephrectomy.

The third case is that of infected hydro-ureter with reflux in healed tuberculosis which acted as a vesical diverticulum with urinary residual and chronic infection.

The fourth case is that of a primary transitional cell carcinoma of ureter occurring 27 years after nephrectomy, the second case of primary ureteral carcinoma of ureteral stump to be recorded.

Ureterectomy in all cases produced cure.

We believe the following points warrant emphasis:

Disease of the ureteral stump may become manifest years after nephrectomy. In all four of our cases symptoms and positive urinary findings were absent for 11, 13, 17 and 27 years after nephrectomy.

The ureteral stump is subject to varied pathological changes including primary neoplasm and many cases escape recognition even by the examining urologist.

The clinical significance of the ureteral stump as a site of urinary tract disease should be emphasized. Urologic study of all nephrectomized patients should include investigation of the ureteral stump. Where catheterization of the ureteral segment cannot be accomplished, satisfactory ureterograms can frequently be obtained by injecting media into ureteral meatus through a bulb catheter. Cystography may also add information where radiographic demonstration cannot be obtained by catheterization.

The possibility of existent disease in a ureteral stump which has stenosed to a point defying demonstration by catheterization and retrograde injection is to be considered.

The indications for concomitant ureterectomy should be carefully evaluated by the surgeon in every candidate for nephrectomy.

CONCLUSIONS

Two cases of pyo-ureter secondary to ureteral obstruction occurring 11 and 13 years after nephrectomy are presented.

One case of pyo-ureter secondary to ureteral reflux occurring 17 years after nephrectomy for tuberculosis is presented.

One case of primary ureteral carcinoma occurring 27 years after nephrectomy is presented, the second case of neoplasm in the ureteral stump to be reported in urologic literature.

The ureteral stump warrants careful scrutiny in all nephrectomized patients undergoing urologic study.

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PRIMARY CARCINOMA OF THE URETER: A PATHOLOGIC AND PROGNOSTIC STUDY

GERALD F. WHITLOCK, JOHN R. McDONALD* AND EDWARD N. COOK*

This is a pathological study, with special reference to prognosis, of 33 cases of primary carcinoma of the ureter from patients treated surgically at the Mayo Clinic up to 1945. The clinical aspects of 27 of the 33 cases have been previously reported by Cook, Counseller and Seefield. It includes six previously unreported cases. It represents a relatively large series when it is considered that, at last count, there have been only 312 reported cases in the literature.

In this study we wish to: 1) present a practical and much needed classification of ureteral carcinoma based on histopathologic structure; 2) determine the incidence of the various types and grades of tumor; 3) attempt the determination of vein and lymphatic involvement; 4) correlate the incidence of carcinoma of the bladder before and after operation for removal of ureteral tumors; and 5) correlate the postoperative fate of patients with the type of tumor present.

PROCEDURE

Our material consisted of the preserved gross operative specimens, available in 25 of the 33 cases, which usually consisted of the kidney, the entire ureter and frequently a small segment of bladder surrounding the intramural ureter. In the remaining 8 cases, the original microscopic sections were utilized in lieu of the gross specimens.

After first determining and recording the number, size, location and gross appearance of each ureteral tumor, blocks of tissue were cut in such a manner that the sections were representative of the entire tumor and full thickness of the ureteral wall. This allowed us to study the underlying and adjacent ureter for submucous and muscular infiltration and for involvement of the ureteral veins and perineural lymphatics. A typical "whole section" of a papillary ureteral tumor is illustrated in figure 1, *A*.

A careful microscopic study was then made on each tumor without prior recourse to the clinical history and without prior knowledge of the fate of the patient. After completion of the histopathologic study the clinical histories were reviewed for pertinent clinical data and follow-up letters were sent to all patients still surviving to determine their subsequent course.

CRITERIA

Any classification of ureteral tumors, to be accurate and complete, must include the structural type (i.e., its papillary or nonpapillary character), the presence or absence of infiltration, the cell type, and the cellular grade or degree of anaplasia registered in the tumor cells themselves.

Study of this group of tumors suggested the use of the workable classification

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previously presented by McDonald and Priestley in their study of 75 cases of carcinoma of the renal pelvis. It is similar, but not identical, to the grouping adopted by the Committee for the Carcinoma Registry of the American Urological Association for carcinoma of the urinary bladder.

The classification of ureteral tumors used in this study is as follows:

A) Papillary carcinoma, grades 1, 2, 3
B) Papillary and infiltrating carcinoma, grades 2, 3, 4
C) Nonpapillary infiltrating carcinoma, grades 2, 3, 4

In addition, the cell type (transitional cell or squamous cell) is appended. The method of Broders was used for the estimation of the cellular grade. In actual usage there will be found to be no grade 1 infiltrating tumors and no grade 4 purely papillary tumors. It should be emphasized that the papillary or nonpapillary character of a tumor is a microscopic and not a gross diagnosis.

The importance of dividing tumors into papillary and nonpapillary types is

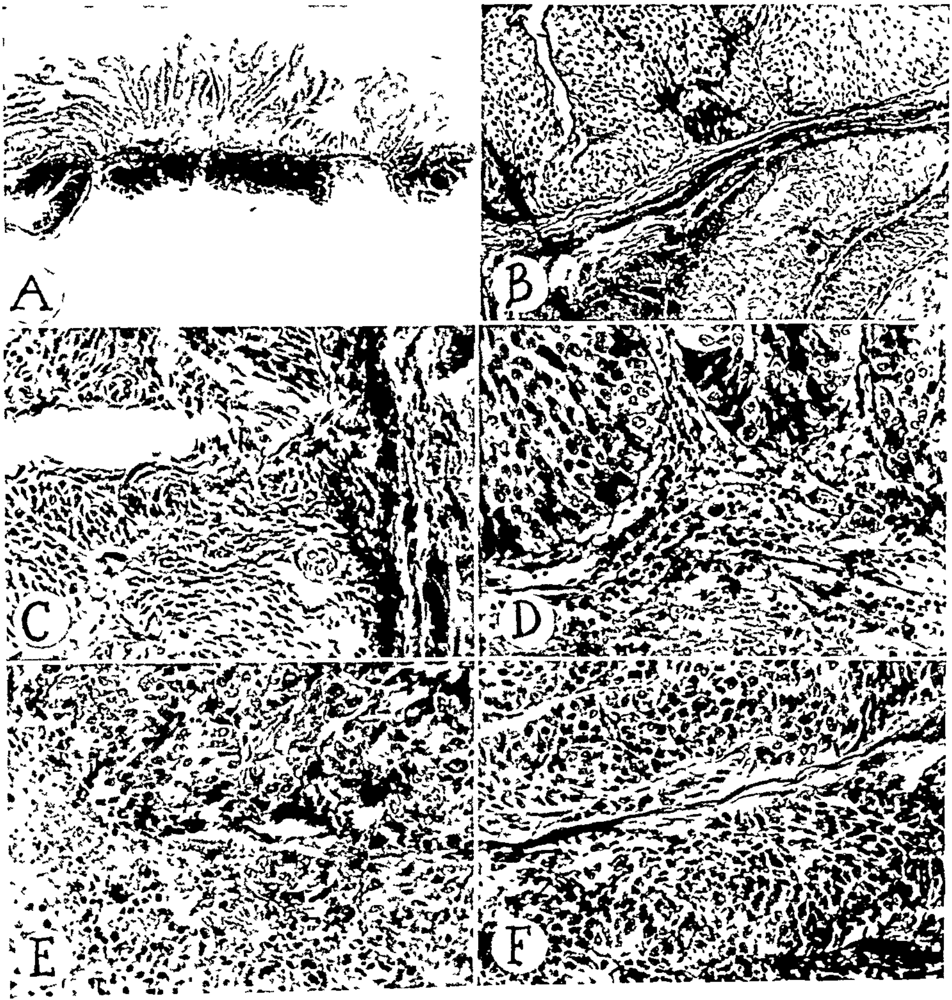

FIG. 1. *A*, low magnification of "whole section" of papillary carcinoma of ureter. *B*, papillary carcinoma of ureter, grade 1. *C*, papillary carcinoma of ureter, grade 2. *D*, papillary carcinoma of ureter, grade 3. *E*, papillary and infiltrating carcinoma of ureter, grade 3. *F*, papillary and infiltrating carcinoma of ureter, grade 4.

shown in this and in previous studies by the propensity of papillary tumors to form multiple or recurrent growths in other parts of the urinary tract; whereas, nonpapillary tumors do not exhibit this tendency. The importance of determining the presence or absence of infiltration is shown in this study by the marked differences in life expectancy.

Papillary carcinomas are shown in figure 1, *B*, *C*, *D* which respectively show grades 1, 2, and 3 tumors. This type of tumor literally sits on the surface of the ureteral mucosa. The basement membrane is intact and there is no involvement of the submucous or muscular layers of the ureter by tumor cells. We found no evidence of vein or lymphatic involvement in the group of papillary tumors.

Papillary and infiltrating carcinoma, grades 3 and 4, are exemplified in figure 1, *E* and *F*, respectively. These tumors are papillary on the surface but exhibit roots of neoplastic cells invading the muscularis of the ureter.

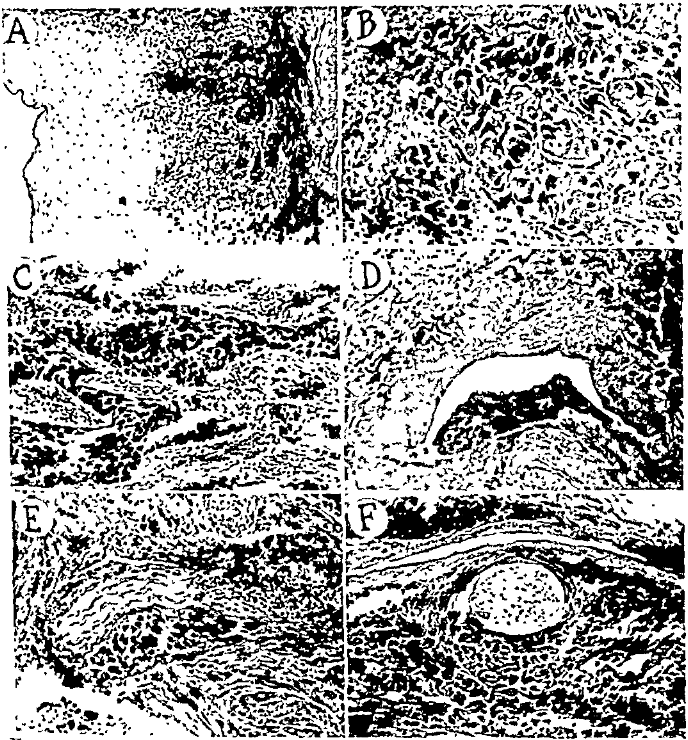

FIG. 2. *A*, nonpapillary infiltrating squamous carcinoma of ureter, grade 3. *B*, same tumor as in *A*, showing invasion of deeper layers of ureteral wall. *C*, nonpapillary infiltrating, ulcerated, transitional carcinoma of ureter, grade 4. *D*, tumor cell thrombus in ureteral vein. *E* and *F*, tumor cells from an infiltrating carcinoma, grade 3, filling perineural lymphatic vessels.

Nonpapillary infiltrating carcinoma is typically represented in figure 2, *A* which shows a squamous cell carcinoma with cornified epithelium covering highly malignant cells in the basal layer. Figure 2, *B* shows infiltration of the ureteral wall by this same tumor. Figure 2, *C* shows a flat, ulcerated, nonpapillary tumor, grade 4.

In both the papillary and infiltrating and the nonpapillary infiltrating groups, it was frequent to see tumor cell thrombi in the ureteral veins (fig. 2, *D*) and involvement of the perineural lymphatics (fig. 2, *E* and *F*).

ANALYSIS OF CASES

Sex. Twenty seven of the 33 patients were male and six were female, a ratio of four males to one female.

Age. The age of the patients is summarized in table 1. Twenty five of the 33 cases were between 50 and 70 years of age. This is in agreement with previous tallies which show the greatest incidence of carcinoma of the ureter in the sixth and seventh decades of life. The youngest patient was a man of 37 years.

Location of tumor. The site of the growth in this series is shown in table 2. The left side was involved 21 times and the right side 12 times. This is not in keeping with previously reported series which have shown the right side to be more frequently involved. Nineteen, or more than one half of the tumors, involved the lower third of the ureter alone. Scott states that about one half of the cases show involvement of the lower one third of the ureter.

It is interesting to note that in 10 cases where the tumor occupied the lower ureter, a portion of the tumor could be seen protruding from the ureteral meatus at the time of cystoscopic examination.

TABLE 1. *Carcinoma of ureter: Age of patients*

Age of Patient	Number
30–39	2
40–49	3
50–59	11
60–69	14
70–79	3
Total	33

TABLE 2. *Carcinoma of ureter: Site of growth*

Portion of ureter	Rt. ureter	Lt ureter	Total
Upper ⅓	3	2	5
Middle ⅓	1	0	1
Lower ⅓	5	14	19
Lower and middle ⅓	1	2	3
Upper and middle ⅓	0	0	0
Upper and lower ⅓	1	3	4
Entire ureter	1	0	1
Total	12	21	33

TABLE 3 *Carcinoma of ureter Multiple growths*

Location of tumors	Type	Grade
6 tumors—entire ureter	All papillary	All gr 1
1 in upper 1/3 1 in lower 1/3	Both papillary	Both gr 2
1 in upper 1/3 1 in lower 1/3	Both papillary	Both gr 3
1 in upper 1/3 1 in lower 1/3	Both papillary	Both gr 3
2 in upper 1/3 1 in lower 1/3	All papillary and infiltrating	All gr 3
1 in U P juncture 1 in upper 1/3	Pap & infilt Papillary	Grade 3 Grade 1

Multiple growths Multiple, separate tumor growths in the ureter occurred in 6 patients (table 3) All six of the tumors forming multiple growths were of a papillary structure, although two of them also showed evidence of infiltration (both grade 3 tumors) In no instance of a flat, nonpapillary growth were there multiple growths This evidence represents one reason why the division of ureteral carcinomas into papillary and nonpapillary forms is practical

Associated bladder tumors Further evidence of the frequency with which papillary tumors are associated with multiple growths is seen in those cases exhibiting tumors of the bladder prior to or after operation for the removal of a primary carcinoma of the ureter With the exception of one case, all of the patients in this series underwent a preoperative cystoscopic examination Postoperative, follow up cystoscopies were carried out, one or more times, in 23 of the 33 patients Despite the fact that "recurrence" in the group of 10 cases not followed by cystoscopy is unknown, there still were 14 cases in which carcinoma of the ureter was associated with one or more carcinomas of the bladder In nine of these 14 patients the ureteral neoplasm was a papillary lesion, in five it was papillary and infiltrating, and in none was there a nonpapillary growth

In one case the patient had undergone endoscopic destruction of recurrent bladder tumors nine times before a papillary, grade 3 carcinoma of the ureter was discovered Since removal of the latter, he has had no further bladder tumor recurrences on numerous follow up cystoscopies

On the other hand, in another case, bladder tumors were present on two occasions prior to removal of a papillary, grade 2 carcinoma of the ureter and recurrences in the bladder have been noted at six successive postoperative cystoscopies at three month intervals

In 10 instances, carcinoma of the bladder developed after surgical removal of a primary carcinoma of the ureter, sometimes years afterward

Types and grades of tumors (See table 4) In two of the 33 cases, the tumor was

TABLE 4. *Carcinoma of ureter: Incidence of types and grades*

Grade	Type unclassifiable	Papillary	Papillary & Infiltrating	Infiltrating	Total	
					No.	% of 33
1	0	4	0	0	4	12.1%
2	1	10	1	1	13	39.4%
3	1	3	5	2	11	33.3%
4	0	0	3	2	5	15.2%
Total	2	17	9	5	33	100.0%
% of 31 tumors classifiable by type		54.9%	29%	16.1%		100.0%

not classifiable as to structural type. In one instance, insufficient tissue was available. In the other, there was a huge inoperable mass which defied determination of the original type.

Seventeen (54.9 per cent) of 31 tumors classifiable as to type showed a purely papillary structure. Nine (29 per cent) were papillary and infiltrating tumors. Five (16.1 per cent) were primarily infiltrating carcinomas with no evidence of papillary structure. All of the latter were associated with extensive invasion and metastases.

All 33 tumors admitted of grading on a histological basis. Four tumors were graded 1 (12.1 per cent), 13 tumors were graded 2 (39.4 per cent), 11 tumors were graded 3 (33.3 per cent), 5 tumors were graded 4 (15.2 per cent). Taking the group as a whole, about one half were of high grade malignancy (grades 3 and 4) and about one half were of low grade malignancy (grades 1 and 2).

Correlation of type with grade of malignancy. Fourteen (82.3 per cent) of the 17 papillary tumors were of low grade (grades 1 and 2). All of the grade 1 tumors and all but two of the grade 2 tumors were purely papillary in character, showing no evidence of infiltration. With the exception of these two grade 2 tumors, all of the neoplasms in the two groups showing infiltration were of high cellular grade (grades 3 and 4). It is interesting to note that three of the papillary tumors were sufficiently undifferentiated as to be classified as grade 3 malignancies on a cellular basis and yet had shown no infiltration at the time of their surgical removal.

Vein and lymphatic involvement. Involvement of the peri-ureteral veins, the perineural lymphatics, or both was found in only 5 instances by the method used in this study. Yet, in 3 cases in which the patient died a few months later with known metastases no evidence of involvement of the veins or lymphatics was found in the microsections, as prepared.

Another case in which no objective evidence of lymphatic involvement could be found in the microsections was seen to have lymph nodes filled with cancer at the time of surgical exploration.

The conclusion, therefore, is that the method of study used in this investigation does not offer an accurate index of the actual incidence of vein and lymphatic involvement. It is possible that if the entire ureter were to be cut into serial sections, that, somewhere along the line, lymphatic or venous involvement would be found in many cases in which such involvement is not evident in one section. Obviously, however, such a procedure is not practical day by day in the surgical pathological laboratory.

Nevertheless, it is apparent that where such involvement is demonstrable, the prognosis is grave. The length of survival following operation in the 5 cases was, respectively, 7 months, 8 months, 3 months, 7 months and 13 months.

Such involvement was found in none of the papillary tumors, only in the infiltrating varieties and only with grade 3 or 4 cancers. McDonald and Priestley, likewise, found no venous or lymphatic involvement in the papillary group of their series of renal pelvis tumors.

PROGNOSIS

One patient represented a postoperative death for a hospital mortality rate of 3 per cent. *Tables 5 and 6 show the 3 and 5 year survival rates, respectively, of* patients with carcinoma of the ureter according to the histologic type of carcinoma. It is obvious that the three histologic types are attended by marked differences in life expectancy.

Papillary. Of the 17 patients with purely papillary carcinoma, twelve had been operated upon at least 3 years before the date of inquiry. Of these, nine (81.5 per cent) were living three or more years after operation. Ten of the seventeen had been operated upon five or more years at the date of inquiry; seven (66.7 per cent) survived five or more years after operation.

TABLE 5. *Carcinoma of ureter: Three year survival rates according to type of carcinoma*

Type of Tumor	No. of pts operated upon 3 or more yrs before inquiry	Patients who survived operation		Lived 3 or more years after operation	
		Total	Traced	No	% of traced patients
Papillary	12	11	11	9	81.5%
Papillary and infiltrating	7	7	7	1	14.3%
Infiltrating, nonpapillary	3	3	3	0	
Total	22	21	21	10	47.6%

TABLE 6. *Carcinoma of ureter: Five year survival rates according to type of carcinoma*

Type of Tumor	No of pts operated upon 5 or more yrs before inquiry	Patients who survived operation		Lived 5 or more years after operaton	
		Total	Traced	No.	% of traced patients
Papillary	10	9	9	6	66.7%
Papillary and infiltrating	7	7	7	1	14.3%
Nonpapillary infiltrating	2	2	2	0	
Total	19	18	18	7	38.8%

TABLE 7. *Carcinoma of ureter: Three year survival rates according to grade of malignancy*

Grade of Tumor	No. of pts. operated upon 3 or more yrs. before inquiry	Patients who survived operation		Lived three or more years after operation	
		Total	Traced	No.	% of traced patients
1 and 2	11	11	11	10	90.9%
3 and 4	11	10	10	0	
Total	22	21	21	10	47.6%

TABLE 8. *Carcinoma of ureter: Five year survival rates according to grade of malignancy*

Grade of Tumor	No. of pts. operated upon 5 or more yrs. before inquiry	*Patients who survived operation*		*Lived five or more years after operation*	
		Total	Traced	No.	% of traced patients
1 and 2	9	9	9	7	77.8%
3 and 4	10	9	9	0	
Total	19	18	18	7	32.8%

Five of the 17 patients did not lend themselves to statistical evaluation because their operation had been less than 3 years at the date of inquiry. All were living and well from 1½ to 2 years following surgery.

Papillary and infiltrating. Of the 9 patients with papillary and infiltrating carcinoma, all were dead in less than 3 years after operation except one. Interestingly, his was the only low grade neoplasm in the entire group of papillary, infiltrating carcinomas. He had survived 10 years at the time of last inquiry, but showed evidence of extensive tumor recurrence in the pelvis and abdomen at that time. The average length of survival of those who died was 13 months.

Nonpapillary, infiltrating. None of the 5 patients with nonpapillary, infiltrating carcinomas lived as long as 2 years, including those operated upon so recently as to be not included in tables 5 and 6. The average length of survival was 10 months.

Prognosis by grade. It is also apparent that marked differences in life expectancy occur with the grade of the malignancy (tables 7 and 8). Of the patients with a grade 1 or a grade 2 neoplasm, 90.9 per cent lived three or more years and 77.7 per cent lived five or more years after surgical removal of their ureteral tumor. On the other hand, no patient with a grade 3 or grade 4 malignancy lived as long as 3 years. Noteworthy is the fact that the only low grade cancer (grade 2) of a nonpapillary infiltrative type killed its host in 9 months after operation.

CONCLUSIONS

A workable classification of carcinoma of the ureter is presented which has practical prognostic significance. It is based on the pathological study of 33 cases and is similar to classifications already proven useful in carcinoma of the renal pelvis and urinary bladder.

In this series, 55 per cent of the tumors were purely papillary in structure, 29 per cent were papillary and infiltrating, and 16 per cent were nonpapillary, infiltrating.

About one-half (51.5 per cent) of the ureteral carcinomas were of low histologic grade (grades 1 and 2) and about one-half (48.5 per cent) were of high grade malignancy (grades 3 and 4).

The majority (83.2 per cent) of pure papillary carcinomas were of a low degree of malignancy and the majority of papillary and infiltrating and pure infiltrating carcinomas were of a high degree of malignancy (85 per cent grades 3 and 4).

Vein and lymphatic involvement occurred in this series only with carcinomas showing infiltration. The frequency with which such involvement was found in this study is undoubtedly lower than the actual incidence.

At least one-half of the papillary carcinomas of the ureter were associated with, or followed by, similar carcinomas in the bladder. The nonpapillary tumors did not exhibit this tendency. Of the 33 cases, there were 10 instances in which bladder tumors developed after removal of the primary carcinoma of the ureter. This fact makes it advisable for us to carry out regular, routine postoperative cystoscopic checkups to the same degree that we are now following up cases of carcinoma primarily in the bladder.

The prognosis of low grade papillary tumors of the ureter is good. The prognosis of high grade tumors showing evidence of infiltration is extremely poor. Of the patients with a papillary carcinoma, 66.7 per cent lived 5 or more years. Only one patient with an infiltrating carcinoma lived as long as 3 years and he was not cured. Of the patients with a grade 1 or 2 carcinoma, 77.7 per cent lived 5 or more years. No patient with a grade 3 or 4 cancer lived as long as 3 years. The average length of life of patients who died after operation in the two groups of carcinomas showing infiltration was about 11 months.

It is apparent from the foregoing evidence that the standard operation of complete nephro-ureterectomy, as practiced today, is adequate and satisfactory for the treatment of the papillary types of carcinoma of the ureter.

It is apparent, on the other hand, that we are not curing patients with infiltrating carcinoma of the ureter by present day methods of surgery. Whether more complete dissection of the regional lymphatics would offer a higher rate of cure remains to be seen.

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SPECIAL PROBLEMS OF URINARY CONTROL IN PATIENTS WITH MULTIPLE SCLEROSIS

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Urinary incontinence is a severe handicap to the patient with multiple sclerosis. Even the patient with fairly advanced disease can adjust himself to many of his other difficulties. He can get by with his halting gait or scanning speech and remain active in his family circle. Urinary incontinence, however, causes him to withdraw to the loneliness of his room or wheelchair.

In a previous communication (*J.A.M.A.*, 1954) based on an experience with 85 patients with multiple sclerosis who in addition had urinary symptoms, I was able to show that it was possible, in most instances, to control the disquieting urinary frequency, the urgency, and the incontinence by simple means without resorting to indwelling catheters, penis clamps, or incontinence bags.

In this group, however, there was a small number of patients in whom conservative methods failed to control the symptoms. Additional disease factors affecting the lower urinary tract rendered ineffective the measures that were helpful in the uncomplicated case of multiple sclerosis.

Before discussing these special problems and how to deal with them, it may be wise to review here briefly the character of the bladder lesion in multiple sclerosis and the principles on which the successful management of the ordinary case rests.

The detrusor in multiple sclerosis is markedly hyperirritable and un-coordinated (fig. 1). Minor stimuli that would pass unnoticed by the normal bladder are sufficient to cause sharp contractions of portions or of the entire organ (fig. 2). The commonest stimulus to induce an unwanted detrusor contraction is a sudden increase in intra-abdominal pressure that results from efforts such as rising from the recumbent or sitting position, lifting weights, climbing stairs, or stepping onto or off curbs. The sudden detrusor contractions are responsible for the precipitous urgency and the involuntary micturition in multiple sclerosis. To inhibit the detrusor contractions the levator ani including the pubococcygeus must be quickly contracted. The patient with multiple sclerosis, however, cannot readily do this. He is just as awkward in the control of his levator ani as he is in the control of his leg muscles, an awkwardness that leads to his peculiar gait.

The neurogenic bladder of multiple sclerosis moreover is subject to spontaneous and recurrent infections. Acute or chronic cystitis is an added powerful stimulus to the detrusor. Elimination of the infection is, therefore, an important part of the management of the bladder in multiple sclerosis.

The function of the neurogenic bladder of multiple sclerosis can be improved 1) if the bladder is shielded against unnecessary stimuli to reduce urgency, 2) if the detrusor hyperirritability is reduced to eliminate incontinence, and 3) if the bladder capacity is increased to lessen frequency and nocturia. Clinically, this is

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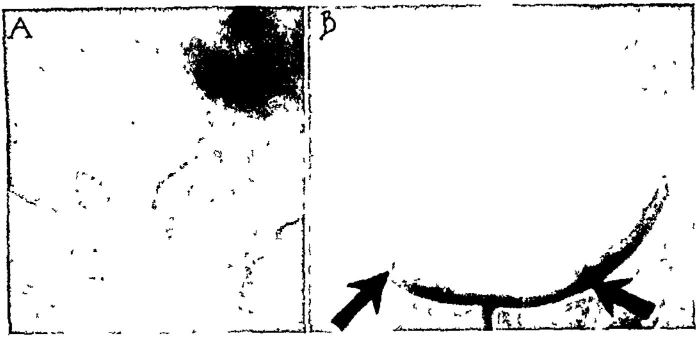

Fig. 1. *A*, note hyperirritability of detrusor. Bladder could not be filled beyond small capacity. *B*, cystogram obtained during excretory urography. Arrows point to segmental contractions of detrusor

accomplished by regulating the patient's activity so as to obviate needless efforts ("effort incontinence" is typical of multiple sclerosis) which tend to increase intra-abdominal pressure suddenly. The fluid intake must be limited to physiologic needs. Forcing of fluids causes unnecessary urinary frequency. The hyperirritability of the detrusor can be decreased and the bladder capacity can be increased for hours at a time by the judicious use of anticholinergic drugs (fig. 3). Of these atropine sulfate, gr. 1/150 (0.4 mg.), is the cheapest and often the best. The patient is taught to note the length of time it takes for the drug to take effect and the duration of the effect. The drug is then administered in a way to secure detrusor relaxation for the desired period of time during the day and it can be used at night to eliminate nocturia and enuresis. If atropine is not tolerated another of the many available anticholinergic drugs must be tried.*

The foregoing measures will satisfactorily control the urinary frequency, the urgency, and the incontinence in the uncomplicated case of multiple sclerosis affecting the bladder.

In the 8 cases that form the basis of this report, this regimen was unsuccessful. In each, complicating factors affecting the lower urinary tract created a special problem and had to be dealt with first before the urinary symptoms could be brought under control. A brief description of these 8 cases including their management will illustrate this point

CASE REPORTS

Case 1. M. P., a man aged 69, BIH record No. M22799, had multiple sclerosis for 5 years and marked urinary frequency, urgency, and incontinence He had to use a penis clamp for the control of incontinence. A large bladder stone and benign prostatic hypertrophy were found on examination in addition to his multiple sclerosis. The stone and the enlarged gland were removed suprapubically. After the postoperative cystitis had cleared, excellent control was obtained with atropine, regulation of fluid intake, and adjustment of his mode of living. He has not needed the penis clamp since (fig. 4).

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* Bellafoline or octin can be used as a substitute for the atropine Banthine too can relax the detrusor but in our cases we found it difficult to obtain constant results with it It either relaxed the bladder too much or not enough

Case 2. R. A. B., a man aged 59, BIH record No. 96108, had multiple sclerosis for 8 years and urgency, frequency, and incontinence for past 6 months. His anal sphincter was found to be somewhat relaxed and the prostate was enlarged to 2 plus, typical of benign prostatic hypertrophy. The cystogram showed elevation of the bladder base by the enlarged gland. In September 1953, he had sudden urinary retention which recurred after catheterization. He was taken to another hospital where transurethral resection of the prostate was done. A short time later he returned to the hospital because the operation failed to control his symptoms which now seemed to him to be even worse. It was only necessary to clear the urine, to limit his fluid intake, and to teach him to use atropine to suit his needs for symptoms to be relieved.

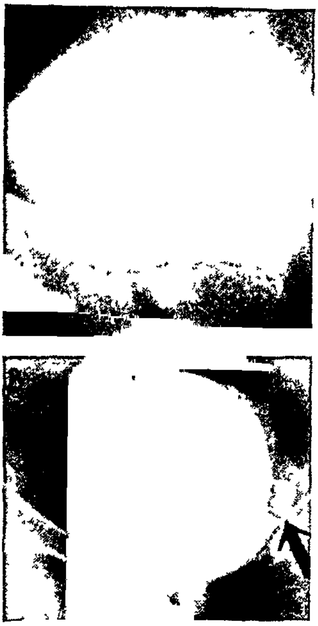

FIG. 2. *A*, bladder during repose. *B*, bladder during micturition. Note pseudodiverticula (arrows) which formed as bladder contracted.

Case 3. L. G., a man aged 56, BIH record No. A4770, complained of urinary frequency and nocturia which became worse during past 6 months. Multiple sclerosis had been recognized 3 years before admission. On examination benign prostatic hypertrophy was found in addition to multiple sclerosis. In January 1947, the enlarged gland was removed suprapubically. He made a good postoperative recovery, but despite this, the urgency, frequency, and incontinence persisted. The patient was operated on at a time when the specific measures to control the bladder symptoms in multiple sclerosis were as yet not in use at the hospital. His postoperative course points up the fact that mere removal of an obstructing prostate in a patient whose bladder is affected by multiple sclerosis is not sufficient to relieve him of his symptoms.

Case 4. R. G., a man aged 35, BIH record No. M10228, had multiple sclerosis

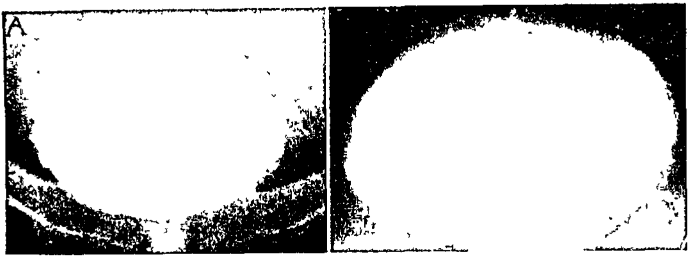

FIG. 3. Effect of atropine sulfate on bladder of multiple sclerosis. *A*, note irritable bladder. Opaque medium instilled under very low pressure elicits detrusor contraction and fluid is voided around catheter. *B*, same bladder 20 minutes after administration of atropine sulfate, gr. 1/150 sc. Note increased capacity and less of spasticity. Bladder can now be filled in normal fashion.

for 6 years and urinary incontinence, urgency, and frequency for the past 2 years. On examination the bladder was found to extend to the umbilicus and contained 1800 cc urine. Adequate micturition could not be established by conservative measures. Transurethral resection of the vesical neck was then done. At the time of his discharge from the hospital the patient voided in quantities of 150 cc. The bladder residual was reduced to 30 cc. This patient has been lost to follow-up after he left the hospital.

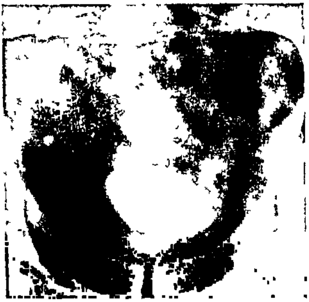

FIG 4. Patient with multiple sclerosis with benign prostatic hypertrophy and large bladder stone. (X-ray of kidneys, ureters and bladder showing bladder stone.)

Case 5. M. S., a man aged 52, BIH record No. M47042, had advanced multiple sclerosis which was first detected in 1943. For the past few years he had attacks of urinary retention, frequency, urgency, and incontinence. On examination his rectal sphincter was found to be relaxed and the prostate was of normal size. While in the hospital he had urinary retention which was irreversible. In December 1953, his vesical neck was resected transurethrally. At the time of his discharge in January 1954, he did not need the catheter and voided fairly well.

Case 6. R. W., a woman aged 53, BIH record No. M39078, had multiple sclerosis for 7 years and urinary incontinence, urgency, frequency, and nocturia for the past 3 years. She often lost urine imperceptibly while walking. Bladder

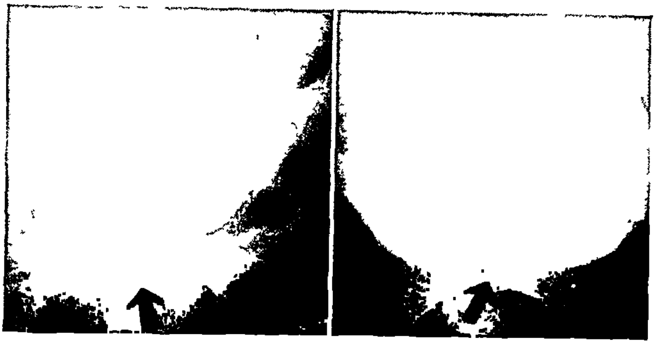

FIG. 5. *A*, arrow points to funnelled vesical neck. Uncontrollable incontinence. *B*, vesical neck after operation. Incontinence now could be controlled.

fluoroscopy showed extra wide funneling of the vesical neck (fig. 5). Her incontinence could not be controlled by conservative measures. On March 17, 1953, the vesical neck was exposed through an incision in the anterior vaginal wall and reefed by means of interrupted mattress sutures. After the catheter was removed postoperatively the patient could not void well, and an indwelling catheter was replaced at intervals for a few months. Thereafter it could be removed permanently and the urine was cleared with appropriate antibiotics. Urinary incontinence, frequency, urgency, and nocturia were remarkably controlled by the use of atropine, regulation of fluid intake, and so forth.

Case 7. P. A., a woman aged 36, BIH record No. 103749, had multiple sclerosis for 10 years and for 3 or 4 years frequency, urgency, and incontinence. During the past few years she had repeated attacks of urinary retention occurring unpredictably during the day or night. Her bladder capacity was larger than normal. Satisfactory micturition could not be achieved by conservative means. In December 1953, the vesical neck was resected transurethrally. After the catheter was removed and the postoperative cystitis cleared, the patient was able to void well, and when last seen on April 8, 1953, she had not needed further catheterizations. Her frequency, urgency, and nocturia were nicely controlled with atropine.

Case 8. H. J., a woman aged 51, BIH record No. M6301, had multiple sclerosis, frequency, urgency, and incontinence for many years and for the past 20 years she had lost large amounts of urine on coughing and walking. The tonus of her rectal sphincter was poor. Her urinary symptoms could not be controlled by conservative means. Bladder fluoroscopy showed the vesical neck to be poorly supported. It could be seen to descend sharply during a cough. In August 1953, the vesical neck was exposed through an incision in the anterior vaginal wall and supported by means of interrupted tantalum mattress sutures. After removal of the catheter and the elimination of the postoperative cystitis, the patient for the first time in many years could control the urine. Urgency, frequency, and nocturia could now be satisfactorily reduced with atropine.

DISCUSSION

Two specific difficulties are encountered clinically in patients who have lower urinary tract disease to complicate the neurogenic bladder of multiple sclerosis.

First, the correct diagnosis may not suggest itself because the urinary symptoms of multiple sclerosis can completely mask the additional disease process Thus a man in whom benign prostatic hypertrophy has developed in the course of his nerve disease may have none of the symptoms characteristic of prostatism and his complaints of frequency, urgency, and incontinence quite naturally could be ascribed to multiple sclerosis This would also be true of the woman who had acquired urinary stress incontinence following childbirth either before or during the course of her multiple sclerosis Second, the mere removal of the obstructing prostate or the correction of the urinary stress incontinence will *per se* not relieve the patient of the urinary symptoms, for there will still be left the effect of the sclerotic nerve lesion on the bladder It is at this point that the principles of management which are useful in the uncomplicated case of multiple sclerosis must be applied for a successful clinical result

Transurethral resection of the vesical neck that was performed in 3 patients merits a word of comment Sudden urinary retention is not uncommon in multiple sclerosis Usually a single catheterization to empty the bladder will enable the patient to void as before Some patients, however, are subject to very frequent and prolonged periods of urinary retention and their bladder becomes distended to hold a liter or more of urine Intermittent catheterizations for patients who are prone to such retention obviously become impractical and of necessity the bladder then has to be drained by an indwelling catheter In this group of patients transurethral resection of the vesical neck, as advocated by Emmett, can restore satisfactory micturition

SUMMARY

The urinary symptoms of multiple sclerosis consisting of frequency, urgency, and incontinence can usually be controlled by conservative measures consisting of the limitation of fluid intake to physiologic needs, the elimination of urinary tract infection, and the use of anticholinergic drugs In patients whose multiple sclerosis is complicated by additional disease affecting the lower urinary tract, this regimen will fail In such cases the presence of the additional disease factors may be difficult to detect because the characteristic symptoms may be masked by those of multiple sclerosis To control the urinary symptoms in these cases a precise appraisal of the status of the bladder and the urethra is necessary If additional disease factors are found they must first be removed and the postoperative cystitis cleared After full recovery from the operative procedure the patient should then be treated by means of anticholinergic drugs and other measures outlined above that are found to be helpful in the uncomplicated case of multiple sclerosis

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THE INTUSSUSCEPTED ILEAL CYSTOSTOMY

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If a continent abdominal cystostomy were made which could be intermittently catheterized, it would be of real use in the treatment of patients with total incontinence. The child with urinary leakage from spina bifida especially needs such an arrangement, since diversion by uretero-intestinal transplantation requires rectal continence as well.

Methods for handling total incontinence have not been very satisfactory. 1) The urine has been collected in rubber appliances but this usually results in severe genital irritation. 2) A permanent urethral catheter is poorly tolerated and introduces infection. 3) The sphincteric action at the vesical neck has been improved in a few cases by plication of the sphincter[1] or by use of a sling of rectus muscle to elevate the bladder neck.[2] 4) The ureters have been transplanted to isolated ileocecal segment,[3] sigmoid,[1] and ileum[4] with varying degrees of continence and functional ability. 5) A permanent suprapubic cystostomy at the proximal urethra has been tried by us, but infection with gradual upper tract damage follows.[1] 6) The suprapubic insertion of a plastic valve[5] has been unsatisfactory for technical reasons.

An alternative solution to this problem occurred to us. We could close the bladder neck and use the bladder itself with its intact ureterovesical valves as the urinary reservoir. A channel then could be constructed to a convenient site on the anterior abdominal wall which would be continent yet allow insertion of a catheter periodically to empty the bladder.

Whether or not a cystostomy would be continent would be based theoretically upon several factors responsible for resistance to urinary outflow: 1) length of the conducting tube, 2) diameter of the tube, 3) tonic contraction of the muscles of the abdominal wall about the cystostomy opening, 4) antiperistalsis if bowel is used, 5) valve formation, 6) angulation, and 7) "sphincter action" by the detrusor at the vesical junction. Using the presence or absence of these factors as criteria, we will describe and evaluate our animal experiments for the formation of a simple continent cystostomy.

Read at annual meeting, American Urological Association, New York, N. Y. June 3, 1954.

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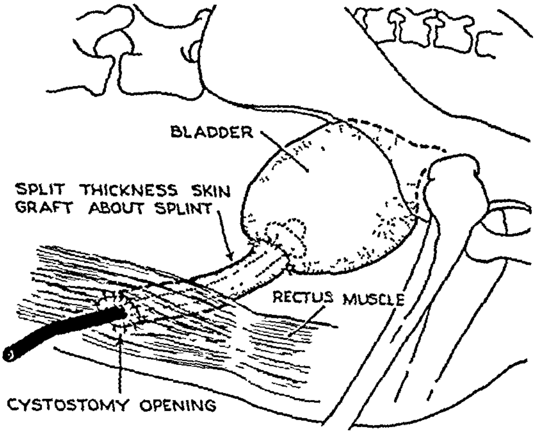

FIG. 1. Schematic outline of split-thickness skin graft cystostomy

EXPERIMENTAL METHODS AND RESULTS

A. Skin graft cystostomy. Split thickness skin grafts have been used in replacing sections of the urethra[6] and recently, esophagus.[7] Continence might be obtained by bringing a skin tube obliquely through the abdominal wall musculature, utilizing tube length and diameter, and muscle tone to retain the urine.

Split thickness dermatome grafts were taken from the dog's chest and sutured about a 24F polyethylene Malecot catheter with the epithelial surface on the inside. These grafts were approximately 8 cm. in length. After exposure through a muscle-splitting right rectus incision, the bladder was opened by a stab wound through which the end of the Malecot catheter was introduced. The graft was then carefully anastomosed to the mucosa, brought out obliquely through the rectus muscle, and approximated to the skin margins (fig. 1). The splinting catheter was then left in place for 6 weeks.

All 3 dogs were completely incontinent after this procedure (table 1) until a stricture had formed sufficient to occlude the lumen. Infection occurred about the splinting catheters, and probably hastened fibrosis and decreased the viability of the grafts. Even if these drawbacks could be overcome, it appears that the tube still would not retain urine. We felt therefore that the factors of tube length and diameter and action of the abdominal muscles were inadequate to insure continence.

B. Janeway-type cystostomy. Since free skin grafts gave poor results, experiments were made to form a tube from a strip of bladder wall, similar to Janeway's gastrostomy. It was hoped that continence might be obtained by placing a tube formed from the full thickness of the bladder wall obliquely through the abdominal musculature, to use detrusor and abdominal muscle tone. Barnes and coworkers[8] have used similar tubes experimentally, in an attempt to produce a spigot which could be clamped for continence.

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TABLE 1. *Continence following various tube cystostomies*

Type of Cystostomy	Incontinent Dogs	Continent Dogs	
Split thickness	3	0	
Janeway	3	0	
Ileocecal	0	2	(Both voided per urethram)
Ileocecal; urethra ligated	0	1	(Overflowed at 300 cc capacity)
Straight ileal cystostomy	0	2	(Voided per urethram)
Straight ileal cystostomy; urethra ligated	2	2	(Continent dogs voided at intervals through cystostomy)
Intussuscepted ileal cystostomy	0	9	(All voided per urethram)
Intussuscepted ileal cystostomy; urethra ligated	0	3	(One dog unable to empty bladder unless catheterized; two voided through cystostomy at long intervals)

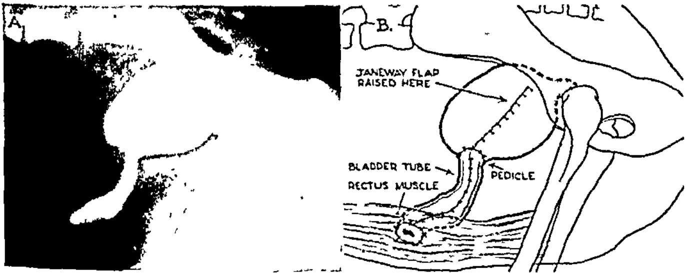

FIG. 2. *A*, cystogram of dog with Janeway cystostomy showing absence of valve. *B*, outline of cystogram.

A lower rectus muscle-splitting incision was made in dogs. The bladder was exposed. Fifty milligrams of banthine intravenously permitted spreading the bladder for incision of an 8 by 2.5 cm. full thickness flap of bladder wall. A tube was formed from the flap around a 20F catheter, and brought out obliquely through the lower rectus muscle (fig. 2) to protrude as a small nipple.

Three dogs subjected to the Janeway-type cystostomy were easily catheterized but all were grossly incontinent (table 1). This showed that the addition of intrinsic muscular contraction from the detrusor to the factors of length, small tube diameter, and contraction of the abdominal wall would not insure continence at normal vesical pressure.

These two sets of experiments indicate that simple tubes made from skin or bladder wall even though placed obliquely through the anterior abdominal wall musculature do not give continence.

C. Ileocecal cystostomy. The ileocecal valve has been used successfully to effect

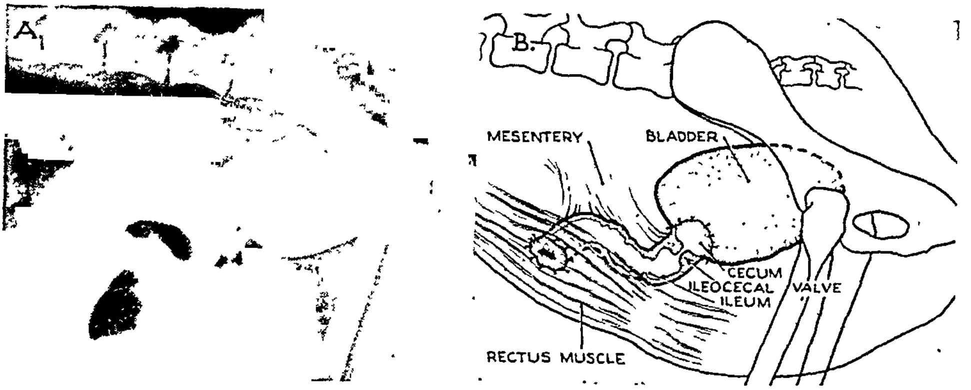

FIG. 3. *A*, cystogram of ileocecal cystostomy showing ileocecal valve adjacent to bladder. *B*, outline of cystogram.

continence after formation of a cecal bladder.[3] This structure seemed promising for a continent cystostomy.

Through a right rectus incision in dogs, after appendectomy, the cecum was sectioned 2 cm. from the ileocecal valve and the ileum divided approximately 12 cm. proximal to the valve, keeping the blood supply intact. Mesenteric attachments were freed enough to allow anastomosis without tension between the cecum and the dome of the bladder. An end-to-end re-anastomosis of the bowel followed. The terminal ileal segment was brought out obliquely through the wound (fig. 3).

Two dogs had ileocecal cystostomy; both were continent and were easily catheterized (table 1). After closure of the vesical neck in one of these animals, continence was maintained until the bladder was overdistended. By adding the factors of *antiperistalsis and a natural valve, continence was achieved.*

The competency of the ileocecal valve has already been demonstrated in this situation.[3] Our experiments, although on only 2 dogs, serve to confirm these findings. We feel that anastomosis of the cecum to the bladder might be of very real value in cases where one would like to increase the bladder capacity in addition to providing urinary continence.

This procedure had several disadvantages in spite of its apparent success. It would require a fairly large surgical procedure in the human subject with the theoretical possibility of requiring a right colectomy because of interference with the local blood supply. For this reason we continued the experimental work in search of a more simple procedure.

D. Straight ileal cystostomy. A continent intestinal fistula can be created by introducing a 12 to 20 cm. antiperistaltic segment of small bowel between the bowel lumen and the skin.[9, 10] We felt that straight ileal cystostomies would tell us the importance of a valve, by comparing them with the ileocecal cystostomy and with the projected intussuscepted ileal cystostomy.

Through a lower rectus incision a suitable segment of terminal ileum was isolated with its attached mesentery. A length of 12 to 15 cm. was used because greater lengths were found to be difficult to catheterize. An end-to-end anastomo-

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[9] Pearse, H. E., Radakovich, M. and Cogbill, C. L.: An experimental study of antiperistaltic jejunal loops. Ann. Surg., **129:** 57, 1949.

[10] Mann, F. C. and Bollman, J. L.: A method for making a satisfactory fistula at any level of the gastro-intestinal tract. Ann. Surg., **93:** 794, 1931.

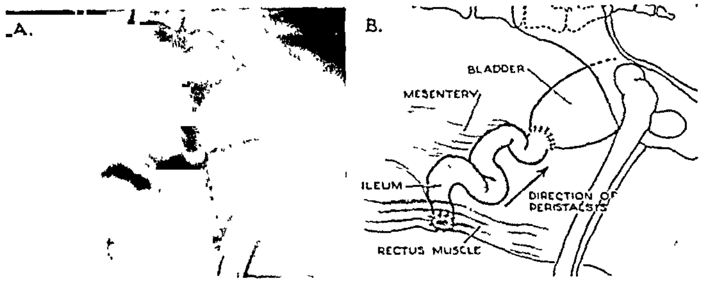

FIG. 4. *A*, cystogram of straight ileal cystostomy. *B*, outline of cystogram

sis re-established ileal continuity. The ileal segment was anastomosed in antiperistaltic fashion low on the anterior bladder wall. This site was selected to avoid angulation of the bowel when the bladder filled. Any angulation would make catheterization difficult. The other end of the segment was then brought out obliquely through the wound (fig. 4).

This antiperistaltic segment of ileum interposed between bladder and abdominal wall produced continence in two dogs at normal voiding pressures (table 1). Antiperistalsis appeared to be the factor of importance, although length and diameter of tube and possibly valve action at the vesical anastomosis may play a part.

The second step of this experiment was closure of the vesical neck, done in 4 dogs. A mushroom catheter was left in place through the cystostomy to allow healing. These catheters were hard to keep in position; the animals could easily extract them. Two of these 4 dogs were completely continent and voided with ease at regular intervals through the cystostomy (table 1). The best explanation for the continence in these 2 dogs, in contrast to the incontinence in the other two, was that they must have had longer effective segments.

A 20 cm. segment of ileum will carry the urinary output in dogs without fatal results.[11] With the different pressure relationships present in the ileal cystostomy, one might expect increase in the re-absorption of urinary constituents. There was a prompt, slight rise in nonprotein nitrogen following the closure of the vesical neck, probably secondary to resorption from the ileal segment (table 2), since once the higher level was reached, there was no further increase. Although there was evidence of cystitis, sometimes with pyelonephritis, in all of these dogs, it is doubtful whether it was the cause of the rise in nonprotein nitrogen, as the rise was not progressive.

E. Intussuscepted ileal cystostomy. Since the length of ileum appeared to be a critical factor, we saw that continence could not be achieved uniformly with peristaltic action alone. If a simple artificial valve could be formed in an ileal segment, continence might well be complete. Basso[12] experimented with a valve created by

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[11] McLean, D. W. and Fais, O. G.: The use of segments of small intestine as ureters. J. Urol., 68: 190, 1952.

[12] Basso, D. E.: The efficacy and applicability of an intussuscepted conical valve in preventing regurgitation and leakage of intestinal contents. Ann. Surg., 133: 477, 1951.

TABLE 2. *Electrolyte resorption from ileal segment*

		Preop.	1 wk.	2 wks.	3 wks.	4 wks.
1. Straight ileal cystostomy with closure of vesical neck						
#79	NPN in mg./100 cc.	19.5	44	45.2	55.0	45.0
	CO_2 in vol. %	45.8	44.5	38.6	39.3	46.7
	Cl^- in mg./100 cc.	490	491	494	496	493
#58	NPN in mg./100 cc.	11.5	38	35.3	43.0	42.5
	CO_2 in vol. %	51.1	65.7	55.6	51.3	50.4
	Cl^- in mg./100 cc.	490	493	493	493	495
#165	NPN in mg./100 cc.	26.2	24.0	20.5	35.5	32.0
	CO_2 in vol. %	46.5	42.6	49.4	45.5	48.1
	Cl^- in mg./100 cc.	487	494	495	496	494
#8	NPN in mg./100 cc.	26.0	31.0	35.0	37.0	39.5
	CO_2 in vol. %	41.7	43.6	39.9	38.3	35.0
	Cl^- in mg./100 cc.	491	492	493	497	492
2. Intussuscepted ileal cystostomy with closure of vesical neck						
#137	NPN in mg./100 cc.	33.5	25.0	27.5	37.0	
	Creatinine in mg./100 cc.	1.5	1.2	1.1	1.2	
	BUN	18.7	16.9	21.5	26.8	
#85	NPN in mg./100 cc.	14.5	33.0	50.1	41.0	41.0
	CO_2 in vol. %	45.1	44.2	47.4	48.4	43.0
	Cl^- in mg./100 cc.	488	492	495	496	493

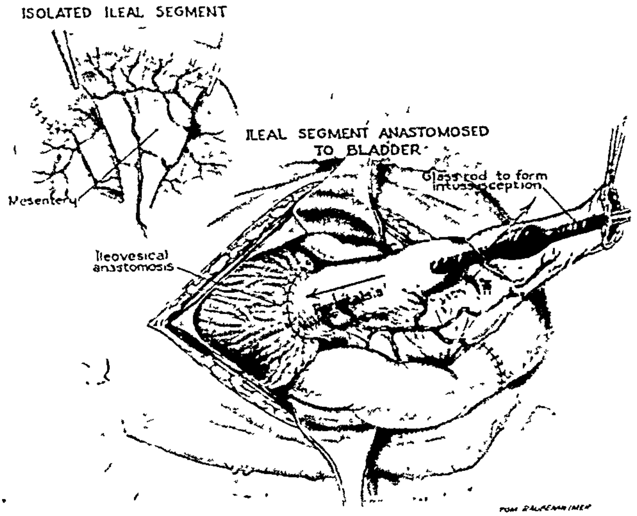
ISOLATED ILEAL SEGMENT
ILEAL SEGMENT ANASTOMOSED TO BLADDER
Glass rod to form intussusception
Mesentery
Ileovesical anastomosis

FIG. 5. Technique of intussuscepted ileal cystostomy I: 1) Isolation of ileal segment, 2) ileovesical anastomosis, 3) intact mesentery to ileal segment, 4) first step in creating intussusception, catgut ligature constricts ileum about glass rod.

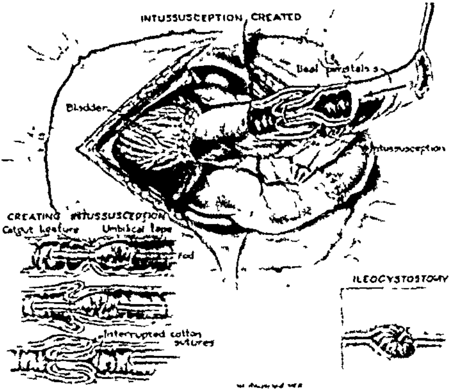

FIG. 6. Technique of intussuscepted ileal cystostomy II: 1) Detail of formation of intussusception: umbilical tape plunger pushes constricted area distally, creating intussusception; serosal margins are securely sutured; 2) cross section of finished valve; 3) completed ileal cystostomy.

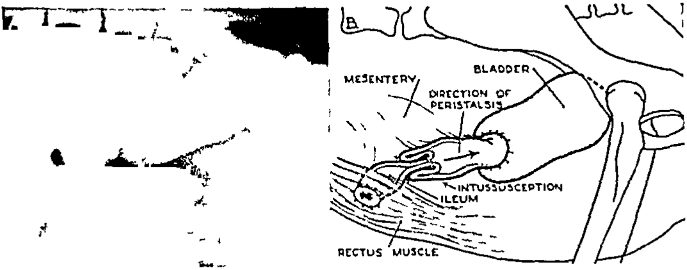

FIG. 7. *A*, cystogram of intussuscepted ileal cystostomy showing lips of valve formed by intussusception. *B*, outline of cystogram.

intussuscepting a short segment of bowel, with suture of the opposing serosal surfaces. He used this in intestinal fistulas and found they were continent to bowel contents and could be readily catheterized.

A simple ileal cystostomy was created in dogs using a 12 to 15 cm. segment of terminal ileum in antiperistaltic position with anastomosis low on the anterior surface of the bladder (fig. 5). In addition, an intussusception approximately 2 to 3 cm. in length was formed in the ileal segment between the bladder and abdominal wall (fig. 6). Catheterization was easiest if the intussusception was formed close to the abdominal wall.

Acute angulation at the site of intussusception occurred in five of these dogs and was directly due to lack of an adequate number of serosal sutures to hold the entire circumference of the intussusception. When enough sutures were used and the opposing serosal surfaces were roughened to encourage adhesions, angulation did not occur (fig. 7). Nine dogs were subjected to intussuscepted ileal cystostomy. All were continent at normal voiding pressures, that is, voided normally through the urethra without leakage from the cystostomy (table 1). Two of the dogs with intact intussusception were subjected to overdistention of the bladder through a catheter. The cystostomy did not leak. The dogs voided through the urethra as soon as the catheter was removed.

The additional factor of an artificial valve added to the antiperistaltic action of the straight ileal segment assured continence.

Three dogs with intact areas of intussusception had subsequent closure of the vesical neck. One of these had to be catheterized, the voiding reflex being insufficient to force urine through the cystostomy. The other two dogs voided at regular intervals through the cystostomy (table 1). It was anticipated that retention of urine would occur in all dogs subjected to closure of the vesical neck. That this did not occur may be partially explained by the very short intussusception present in the two dogs which voided through the cystostomy.

The present study was directed only at developing a completely continent cystostomy. A superfluous but most interesting observation was that certain of the ileal cystostomies were adequate substitutes for the normal urethra, even though no really voluntary sphincter was constructed. These four dogs (Nos. 79, 165, 137, and 85) would void at usual vesical capacities and would completely empty their bladders, proved by the absence of residual urine. Of course, it would be too much to expect this to occur in the human subject.

CLINICAL APPLICATIONS

We are at present applying the intussuscepted ileal cystostomy to children with spina bifida, who have autonomous bladders and atonic urethral and rectal sphincters. It may be applicable as a substitute for ureterosigmoidostomy in other cases of incontinence in which surgical correction at the urethral level has failed. Conceivably it could be applied in the patient with exstrophy by inverting and closing the bladder, leaving the ureteral orifices intact.

Intermittent catheterization appears practical. Two of Gross' patients with sigmoid bladders had a sufficiently tight stoma to give continence. Catheterization was then done intermittently without difficulty.

SUMMARY

Experimental cystostomies were created in 19 dogs.

Attempts in 6 dogs to form straight tubes from bladder to skin with split thickness grafts or with tubes made from the bladder wall failed because of persistent incontinence.

Two dogs had an anastomosis of the cecum to the bladder, bringing the terminal ileum to the skin. The ileocecal valve maintained continence.

Five dogs had a segment of ileum interposed antiperistaltically between bladder and skin. Three were continent, two not leaking even after closure of the vesical neck.

Nine dogs had an interposed ileal segment in which an intussusception was formed. These dogs were continent at normal voiding pressures, voiding through the urethra at usual intervals. Two of these did not leak even with forced overdistention of the bladder. Three of these dogs had closure of the bladder neck; all remained continent.

Some resorption of urinary constituents from segments of terminal ileum 12 to 15 cm. in length was proved by a slight, maintained rise of nonprotein nitrogen. No significant change occurred in the serum chlorides or in the carbon dioxide combining power.

CONCLUSIONS

A continent abdominal cystostomy can be made experimentally in dogs.

The length of the tube, its diameter, and the action of the muscles of the anterior abdominal wall are inadequate alone to prevent leakage.

The antiperistaltic action of an isolated segment of small bowel may be sufficient to assure continence, but a valve gives greater security. The ileocecal valve is effective, but its utilization requires a larger surgical procedure.

Most effective is a simple antiperistaltic ileal segment in which a valve has been formed by an intussusception. These artificial valves hold urine at high vesical pressure, yet are readily catheterized.

It has been possible with antiperistaltic intussuscepted ileal segments to form a nonleaking cystostomy which could be catheterized at regular intervals in a patient with complete loss of sphincter control.

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ADVANTAGES OF TRANSURETHRAL REMOVAL OF CERTAIN BLADDER TUMORS

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Ever since Beer[1] demonstrated that bladder tumors could be entirely destroyed by cystoscopic methods the average urologist has zealously championed this technique. For years it has been thought that the urologist should treat these lesions, not the general surgeon. Some have been very positive in their assertions that most neoplasms of the bladder do not require open surgery, that it is in fact an error so to treat them. Urologists have finally realized that vesical neoplasms are really evidence of a general disease, that they are multicentric in nature and that a visible lesion might be removed while leaving behind other areas of tumor lying below the surface in the opposite wall of the bladder. It certainly seems illogical to open the bladder repeatedly in order to excise tumors. In order to obviate such repetitive procedures some physicians have advocated cystectomy, but radical operation does not attack the root of the problem, for even after removal of the bladder some patients will form growths in their ureters or in the renal pelvis. It has also been shown that, at least in the human, life with an improvised cloaca has certain disadvantages both socially and metabolically. Diverting the urine into the intestine sometimes results in great unhappiness and in general physical and renal deterioration.

Urologists have pointed out that in the great majority of cases tumors of low grade can be completely destroyed at the first sitting and subsequent recurrences (really new growths) can be kept under control by interval cystoscopic examination and fulguration. We believe that in the majority of patients who have a high-grade lesion the best treatment available is transurethral excision of all of the grossly visible tumor supplemented when it seems necessary by irradiation.

We do not decry cystectomy; in an earlier article[2] a series of cases in which the patients were treated at the Mayo Clinic was described in which cystectomy was performed on 117 patients or 9.6 per cent of 1,222 patients treated during the interval 1946 to 1950 inclusive. It was stated in this article: "We have endeavored to advise this operation for those patients in whom the chance of cure was reasonably good and to employ transurethral operations supplemented with radiation therapy for those patients in whom a tumor appeared too extensive to be treated successfully by cystectomy." The conclusion must not be drawn that all of these

Read at annual meeting, American Urological Association, New York, N. Y., June 2, 1954.

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[1] Beer, Edwin: Removal of neoplasms of the urinary bladder: A new method, employing high-frequency (Oudin) currents through a catheterizing cystoscope. J.A.M.A., 54: 1768–1769, 1910.

[2] Thompson, G. J.: The treatment of cancer of the urinary bladder with particular reference to choice of operation. J. Missouri M. A., 49: 813–817, 1952.

patients in whom small lesions were found were submitted to cystectomy. If there seemed to be a good chance of cure of a small lesion by transurethral excision even though it were of high grade, we often chose this method. The type of operation to be used in any case must hinge on consideration of many factors including such things as the general condition and age of the patient. Other important indications have been discussed previously.[3] Not the least consideration is the comparative immediate morbidity and mortality of the different methods of attack, nor the fact that when a tumor has microscopically extended through the bladder wall the 5-year survival rate following either cystectomy or segmental resection is reduced to 5.2 per cent.[4]

This article will discuss a series of 300 cases in which a grade 3 or 4 (Broders' classification) vesical neoplasm was treated at the Mayo Clinic by a transurethral method either alone or in combination with irradiation therapy during the years prior to 1949. The case histories were reviewed and the following pertinent information was recorded: the age and sex of the patient, the location, size, gross appearance and histologic grade of the tumor, the presence or absence of obstruction to the upper part of the urinary tract, the method of treatment employed, treatment of recurrences and the survival period estimated from the time of the initial treatment.

The depth of infiltration of the neoplasm into the wall of the bladder was not always recorded. As a matter of fact this is a difficult observation to make and in most cases must be largely a matter of opinion unless tissue is removed from deep in the wall. Fixation of the wall or lack of distensibility, the presence of a filling defect in the cystogram and the firmness of the tissue as noted by feeling it with the end of the cystoscope are all helpful points in estimating the degree of infiltration.

In the 300 cases in which high-grade tumor was treated transurethrally, there were 3 hospital deaths. The 5-year survival rates of the 297 remaining patients are recorded in table 1. Approximately 100 other cases of high-grade tumor seen during the same interval were omitted from this study for the following reasons: 1) A segmental resection of the bladder wall or a transvesical removal of a neoplasm had been carried out, either at the clinic or elsewhere, previously. 2) The transurethral procedure was employed only for the removal of tissue for microscopic study. 3) There was clinical evidence of distant metastasis at the time of the transurethral procedure. 4) There was associated carcinoma of the prostate gland. 5) A transurethral procedure was employed initially and the decision was subsequently made to resort to an open surgical method.

The estimated size of the tumors determined by cystoscopic examination varied from 0.5 cm. in diameter to huge lesions that involved almost the entire bladder.

Tumors that were located on the base of the bladder, the trigone, the vesical neck, the posterior wall or the dome but accessible to treatment were all included

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[3] Thompson, G. J. Cystoscopic control of vesical neoplasms. In Pack, G. T. and Ariel, I. M. The Treatment of Cancer and Allied Diseases. Ed. 2, New York. Paul B. Hoeber, Inc. (In press.)

[4] McDonald, J. R. and Thompson, G. J. Carcinoma of the urinary bladder. A pathologic study with special reference to invasiveness and vascular invasion. J. Urol., 60: 435–445, 1948.

TABLE 1. *Transurethral removal of malignant neoplasm of the bladder 1948 and earlier: grades 3 and 4; 5-year survival rates by sex*

Sex	Patients		Lived 5 or More Years After Operation	
	Total	Traced	Number	Survival rate, per cent*
Male	234	218	58	26.6
Female	63	55	29	52.7
Total	297	273	87	31.9

* Based on traced patients. Inquiry as of January 1, 1954. Three hospital deaths are excluded in the calculation of survival rates.

The fact that a ureteral orifice was encroached on did not influence the decision to employ or not to employ a transurethral method. In fact this study reveals that when a urogram showed evidence of upper-tract obstruction transurethral operation was preferred at the clinic rather than open surgery. In this series of cases of the 164 patients who had excretory urographic study 76 (46.3 per cent) had obstruction of one or both ureters. In the study by Pool and Cook[5] of the urographic findings in a series of patients who underwent open operation there were 42 (36.8 per cent) who had upper urinary tract obstruction, thus indicating a definite trend toward the use of transurethral surgery if ureteral obstruction is present. This comparison of the urographic findings in the two series of cases seems to emphasize the fact that we did not treat what might be termed the best cases by transurethral operation and the worst by open surgery. It must be clearly recognized that the patient often helps to make the decision as to the type of operation performed; some refuse to have radical treatment even when it might appear to the surgeon to be the method of choice.

TECHNIQUE OF OPERATION

The excision with a resectoscope of a tumor of the bladder has definite advantages over its excision by open surgical methods. One can carefully remove all of the tumor down into what appears to be normal musculature; resection of any tumor proceeds in orderly fashion, excising the growth down to and below the level of the bladder wall and even excavating tissue until all gross tumor is removed. The surgeon must depend chiefly on gross difference in tissue appearance throughout most of the operation. In most cases the border of the tumor is well defined and its homogeneous gelatinous character coupled with its slightly yellow or gray color contrasts sufficiently with the muscle to provide a reliable guide as to depth and extent of operation. Finally the interlacing bundles of muscle can easily be recognized and it seems that no malignant tissue remains. At this stage additional pieces of tissue are excised from the periphery and depth of the area and examined by frozen-tissue methods. If these are negative, the operation is completed. If, however, the tissue is positive, additional strips can be excised until obviously perivesical tissue including fat is obtained by the excursion of the loop. At this point one must be careful not to overdistend the bladder or extravasation of a serious degree can result. If tumor cells have penetrated the bladder wall it seems logical that radiation must provide whatever additional curative measures are possible.

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[5] Pool, T. L. and Cook, E. N.: Urographic study of the upper part of the urinary tract prior to and after cutaneous ureterostomy and ureterosigmoidostomy J Urol , 63: 228–231, 1950.

When a tumor which obstructs the ureteral orifice is excised as the intramural portion of the ureter is freed, the end of the ureter will project into the vesical cavity like a nipple or in a fingerlike fashion.

The excision by open surgical methods of a tumor obstructing the ureteral orifice usually includes a cuff of normal bladder wall and a portion of healthy ureter; the shortened ureter is then reimplanted into another part of the bladder. These operations have not worked out well. As a rule because of stricture or reflux, the kidney ultimately deteriorates in most instances. In contrast following transurethral segmental resection of such a tumor the ureter is left attached in its normal position and the kidney will often improve remarkably. Hydronephrosis will disappear, and the dilated ureter will recede to almost a normal size. If, however, it has been obstructed for many months or a year or more, the kidney will atrophy but it will usually cause no trouble and will remain as a shriveled structure excreting little if any urine of low specific gravity.

When a tumor is located high in the dome or lateral walls or on the anterior wall it is a great aid to have an assistant push down on the abdominal wall (fig. 1). This will bring the tumor down so that it can be easily reached. Gentle finger tip control of the instrument will prevent digging too deeply into the vesical wall. It is usually wise to empty the bladder after excision of three or four pieces. For smooth cutting the electrical unit should be set so that the current has minimal coagulating effect.

POSTOPERATIVE CARE

The bladder should be drained with a one-way Foley catheter; continuous irrigation is not desirable. If the area from which the growth has been excised is very thin or if it is obvious that the perivesical fat has been exposed it might be wise to use continuous suction on the catheter for the first 48 hours. Some pa-

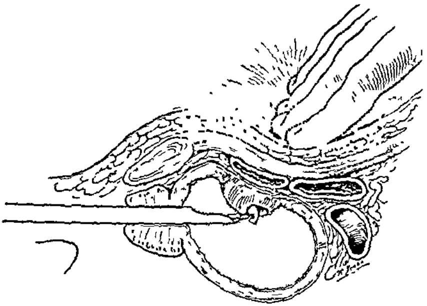

FIG. 1. Method of aiding excision of tumor from anterior wall of bladder.

tients have minimal abdominal pain for a few hours. Catheter drainage should be continued for 5 to 7 days in those cases in which definite perforation of the bladder wall has occurred. Routine use of urinary antiseptics or antibiotics is a wise precaution.

RESULTS OF OPERATION

The immediate improvement of bladder function with relief of frequency and cessation of hematuria and tenesmus is quite striking after transurethral operation. This is particularly apparent when an unusually large growth which has encroached on the vesical cavity or immobilized a large segment of the wall has been removed. In a number of cases not included in this series in which exploration in contemplation of cystectomy revealed gross perivesical extension of tumor, a palliative transurethral resection was later performed which added a great deal to the patient's comfort. In a few of them when combined with irradiation therapy the patients survived 2 or 3 years with good bladder function, finally succumbing to metastasis. In our experience this combination of treatment was tolerated better than either permanent cystostomy or cutaneous ureterostomy.

The bladder wall heals well following removal of extensive tumors, with surprisingly little scar tissue formation or contracture and with no appreciable reduction of bladder capacity. Apparently the mucosa spreads out and covers the denuded area. Cystoscopy months later will show a smooth, elastic surface. In cases in which the ureteral area has been extensively resected the orifice does not stricture but appears instead as an elliptical opening which can be easily catheterized. In no case has it become necessary at a later date to perform nephrectomy because hydronephrosis developed. One patient, in whom a tumor partially obstructed the left ureteral orifice and required resection of it, developed several years later a primary tumor in the lower third of the right ureter and a nonfunctioning right kidney which necessitated nephro-ureterectomy. His left kidney at that time was functioning normally. It is interesting to speculate whether or not it would now be supporting life if instead of transurethral resection of the initial growth a segmental resection with reimplantation of the ureter had been performed.

TABLE 2. *Transurethral removal of malignant neoplasm of the bladder 1948 and earlier; 5-year survival rate by grade of malignancy (Broders); hospital deaths 3/300 = 1 per cent*

Grade	Patients		Lived 5 or More Years After Operation	
	Total	Traced	Number	Survival rate, per cent*
3	210	194	73	37.6
4	87	79	14	17.7
Total	297	273	87	31.9

* Based on traced patients. Inquiry as of January 1, 1954. Three hospital deaths are excluded in the calculation of survival rates.

TABLE 3. *Transurethral removal of malignant neoplasm of the bladder 1948 and earlier, grades 3 and 4, age sex distribution*

Age years	Males		Females		Total	
	Number	Per cent	Number	Per cent	Number	Per cent
30-39	1	0.4	1	1.6	2	0.7
40-49	15	6.3	6	9.5	21	7.0
50-59	49	20.7	13	20.6	62	20.7
60-69	90	38.0	28	44.5	118	39.3
70-79	72	30.4	13	20.6	85	28.3
80-89	10	4.2	2	3.2	12	4.0
Total	237	100.0	63	100.0	300	100.0
Mean	65.4 years		63.3 years		65.0 years	

There were 3 deaths in the hospital following operation. The ages of these patients, all men, were 76, 76 and 71 years. The cause of death in 1 case was cardiac failure on the seventh postoperative day. In another case one ureteral orifice was completely occluded and the other partially at the time of operation, the blood urea being 76 mg. per 100 cc. The tumor was removed but renal function continued to fail and the patient died on the eighth postoperative day. The third patient died of a stroke on the third postoperative day following removal of a large tumor which completely obstructed one ureteral orifice.

Reference to table 1 shows that 31.9 per cent of the traced patients survived 5 years or more. The results in women are about twice as good as in men.

The grade of malignancy is listed in table 2 and the age and sex distribution in table 3. It can be noted that 88.3 per cent of the patients were aged from 50 through 79 years.

IRRADIATION TREATMENT

Of the 297 patients who survived operation 169 (57 per cent) received supplementary x-ray or radium therapy. In our opinion there were a number of patients in whom residual tumor remained after transurethral operation either in microscopic form or in larger grossly visible areas which were deliberately allowed to remain because excision of the tumor was considered too hazardous. Some of these patients have apparently been cured because repeated cystoscopic examinations have revealed no recurrence over a period of 5 or more years and 1 patient is alive more than 17 years after operation.

No attempt will be made in this paper to describe the details of roentgen therapy.

In many of the 169 cases radon emanation seeds were implanted. The method and results obtained in a specially studied series have recently been described by Emmett and Winterringer.[6] In studying the urograms obtained during the examination of the 300 patients comprising our series there were many post-

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[6] Emmett, J. L. and Winterringer, J. R.: Experience with radon seed implantation for bladder tumors. Read at the meeting of the Southeastern Section of the American Urological Association, Palm Beach, Florida, April 12 to 15, 1954.

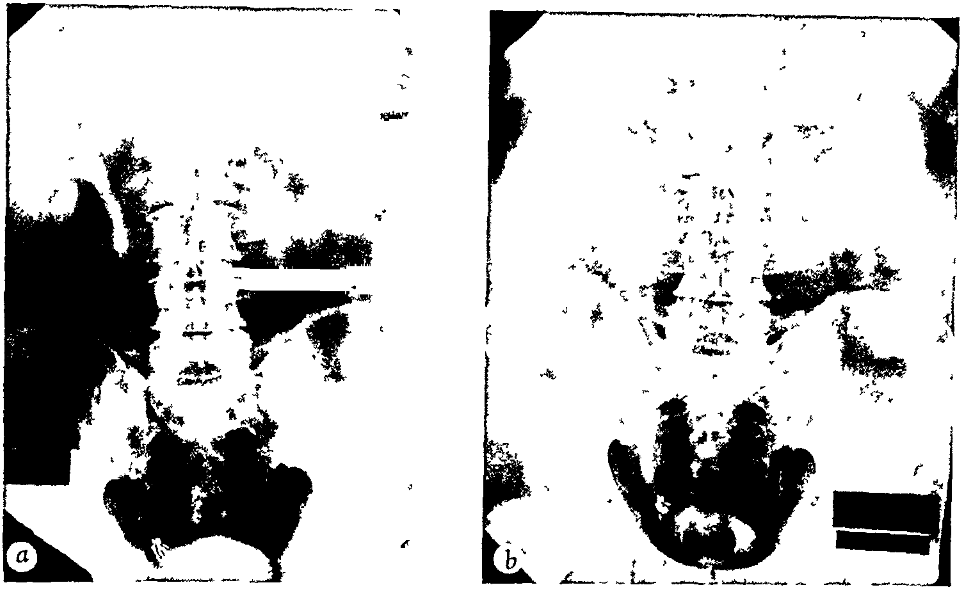

FIG. 2. *a*, These radon seeds were implanted February 16, 1946 Note slight pyelo-ureterectasis apparently due to scar tissue in periureteral area. *b*, Showing almost complete regression of ureterectasis. Kidney pelvis and calyces now normal in size; radon seeds appear to be well beyond bladder.

operative films which revealed that often radon seeds get out into the perivesical tissues either at the time of implantation or subsequently (fig. 2*a* and *b*). As a matter of fact, the deliberate implantation of emanation seeds into the tissues beyond the bladder would not seem amiss because it is in that area that one would like to have some irradiation after the bulk of a growth has been excised with the resectoscope. We never implant radon seeds into that portion of tumor which projects into the vesical cavity.

ILLUSTRATIVE CASES

Case 1.—The patient was a married woman, aged 73 years. On November 1, 1946, a large tumor, which projected into the bladder and superficially infiltrated the region of the right wall including the ureteral orifice, was removed with the Thompson resectoscope. The pathologist reported grade 3 squamous cell epithelioma. There was moderate right ureteropyelectasis, and a definite filling defect could be seen in the excretory cystogram (fig. 3*a*). Convalescence was uneventful. The patient returned in February 1947, when cystoscopy revealed many recurrences in all of the walls of the bladder. These were destroyed by electrocoagulation, and x-ray therapy was advised. This was subsequently given by a radiologist in her home town. The details of it are not available. In June 1947, a minute area of tumor was destroyed cystoscopically. In January 1948, another small tumor was destroyed but none was found in July. In 1949 several small recurrences were destroyed; an excretory urogram showed definite reduction in the degree of hydronephrosis in the right kidney (fig. 3*b*). Throughout 1950, 1951 and 1952 on several occasions small tumors were destroyed, but in the fall of 1953 at the time of the last examination the bladder was entirely negative.

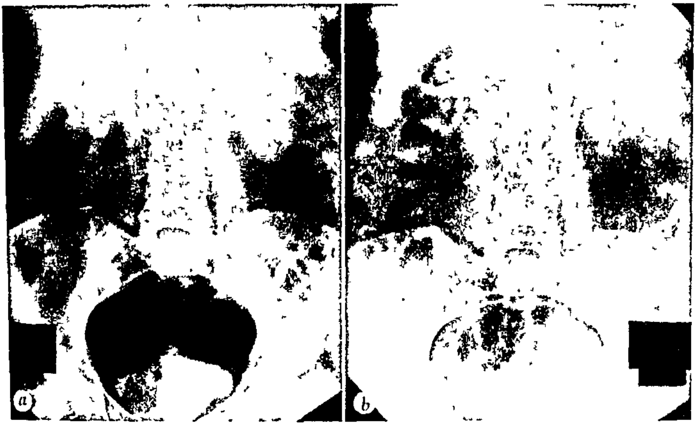

FIG. 3. *a*, Right hydronephrosis; note large filling defect due to grade 3 tumor in right half of bladder. *b*, Note decrease in size of renal calyces and pelvis.

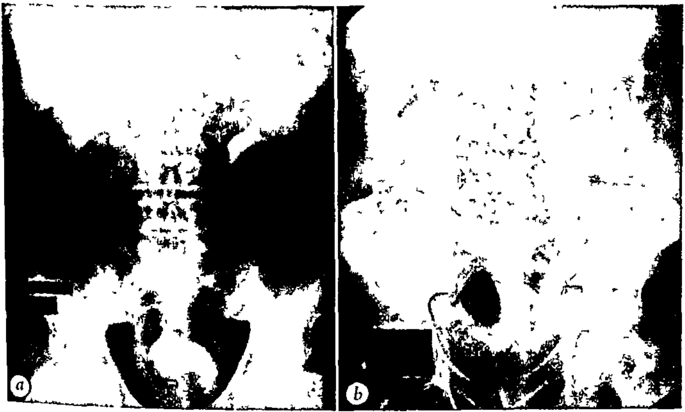

FIG. 4. *a*, Right hydronephrosis, hydro-ureter, large filling defect due to grade 4 tumor in right lateral wall and base of bladder. *b*, Right renal pelvis and calyces now normal in size; cystoscopy showed no recurrence of bladder tumor.

Case 2.—A married woman, aged 89 years, was examined in November 1948, and a tumor 6 by 5 cm. was found in the right posterior and lateral wall of the bladder. The tumor was flat and infiltrating in character, but the bladder wall which surrounded it was soft and flexible. The tumor was excised with the loop resectoscope, exposing normal muscle tissue over the whole tumor area. Only the bleeding vessels were electrocoagulated. The tissue was reported by the pathologist to be grade 3 infiltrating squamous cell epithelioma. The patient was examined in May 1949 and at intervals since that time and no recurrence has been found. She is now in her ninety-sixth year of life.

Case 3. A man, aged 73 years, had a large tumor removed in October 1946. It infiltrated the right side of the trigone, right lateral and anterior wall and extended into the prostatic urethra. The right kidney and ureter showed evidence of obstruction, and there was a large filling defect in the excretory cystogram (fig. 4*a*). A total of 39 gm. of tissue was excised which the pathologist reported to be grade 4 infiltrating epithelioma. Convalescence from the operation was uneventful. The patient was given a course of five x-ray treatments during the interval October 21 to October 25, 1946. In February 1947, cystoscopic examination showed no evidence of bladder tumor, the right ureteral orifice gaped slightly but spurted clear urine. A urogram showed a normally functioning right kidney (fig. 4*b*). The patient was examined in July 1947, and in June 1948, without evidence of recurrence. The bladder wall in the region where the tumor had been removed was soft and smooth and distended readily. In October 1948, the patient returned to the clinic with a complaint of urinary difficulty. Cystoscopic examination showed no recurrence of vesical tumor but the prostate was definitely obstructive and 15 gm. of tissue was removed from it which was reported to be grade 4 adenocarcinoma. The patient remained free of urinary symptoms but died of metastasis 1 year later.

Case 4.—A married woman, aged 65 years, was found to have a tumor 5 by 6 cm. in size attached by a broad base to the left side of the trigone. It was causing partial obstruction of the left ureteral orifice (fig. 5). On August 25, 1947, the growth was removed with the Thompson resectoscope, going well into the bladder musculature. The tissue was reported to be grade 3 papillary squamous cell

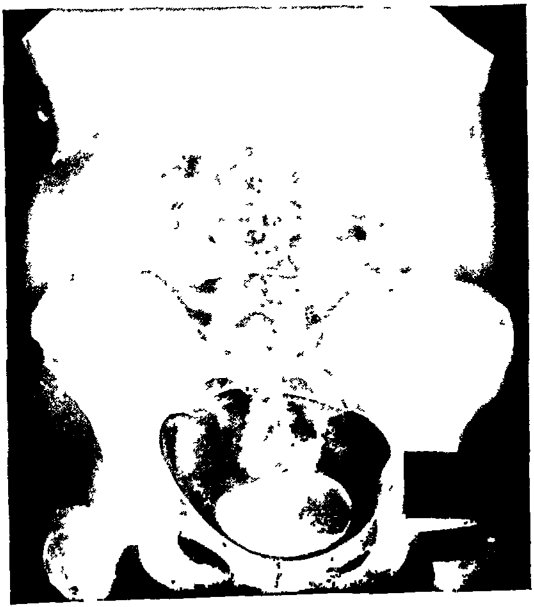

FIG. 5. Large filling defect in left half of bladder due to grade 3 squamous cell epithelioma.

epithelioma During convalescence a course of five x ray treatments was given The patient has returned at intervals since then and there has never been any recurrence of tumor

Case 5 The patient was a man, aged 40 years, from whom a sessile tumor approximately 3 by 4 cm in size was removed on April 21, 1947 The growth was attached to the right lateral wall and was excised with the Thompson resectoscope The pathologist reported that the tissue was grade 1 infiltrating keratinizing squamous cell epithelioma Because of the patient's youth cystectomy was considered but the decision was made not to perform it He was given a course of seventeen x-ray treatments during the interval April 29 to May 17, 1947 The patient has had repeated interval cystoscopic examinations since that time and there has never been any recurrence The last cystoscopy was in January 1954

CONCLUSIONS

We believe that urologists have for years pretty well agreed that in the majority of cases tumors of the bladder of low-grade malignancy can be best removed by transurethral methods

As a result of this study and our experience in recent years we have formed the opinion that a tumor of high grade malignancy which has not infiltrated beyond the bladder wall and which can be accurately delineated is best removed by transurethral operation if such is technically possible

When a tumor has *infiltrated into the perivesical tissues or beyond,* the transurethral removal of its grossly visible portion followed by irradiation therapy intended to destroy the microscopic portions which remain is preferable to open operation

When the extent of a tumor of high grade malignancy cannot be accurately determined with the cystoscope and when tumors of low grade recur with great rapidity both in size and number, transurethral methods of treatment are not advantageous, in such cases cystectomy probably holds more promise of cure

The 5 year survival rate in this series of cases treated by transurethral surgery plus selective irradiation seems better than our results with similar cases which have been treated by open surgical methods

We believe that transurethral excision of vesical tumors combined with irradiation such as is now available with the cobalt bomb apparatus will in time prove superior to all other methods of treatment which have so far been used

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USE OF RADIOACTIVE COBALT (Co_{60}) IN NYLON SUTURES IN TREATMENT OF CARCINOMA OF BLADDER: PRELIMINARY REPORT

VINCENT VERMOOTEN

The management of carcinoma of the bladder remains one of the most difficult urologic problems, if for no other reason than because of the severe morbidity that results. Surgically some types respond to fulguration, some to segmental resection of the bladder and some require total cystectomy with diversion of the urinary stream. Radiologically we have used external radiation with an x-ray machine but more often radium has been used. Young used radium capsules in special applicators through the urethra. Later needles were inserted into the growth or emanations were implanted into the lesion. Attempts have been made to inject the tumor with radioactive gold but I fear that this is not only unsatisfactory but dangerous.

Now we offer a new method of radiation which, in our opinion, is by far the most efficient and most satisfactory method of treating carcinoma of the bladder, especially the extensive, infiltrating type of lesion which is considered either inoperable or requiring total cystectomy. In the few cases we have done, the results have been excellent and the morbidity negligible. As far as we know, this is the first time that this type of radiation has been used in the treatment of carcinoma of the bladder.

In November 1952, a 45 year old man, J. F., was referred to me with a very extensive carcinoma of the bladder. He gave a history of pain at the end of the penis a year before. He consulted his doctor who gave him symptomatic relief by prostatic massage. Six months before being referred to me, he began to have some frequency of urination and urgency which gradually increased until he was voiding every half hour during the day and at least every hour at night. A month previous to my seeing him, he began to urinate blood and bloody mucus. Sometimes the blood was bright red, sometimes dark brown. Frequently his urine contained no blood. Cystoscopic examination showed an extensive, infiltrating type of carcinoma of the bladder involving most of the floor of the bladder and the left lateral wall almost to the air bubble. The left ureteral orifice was also involved. Excretory urograms revealed a small, contracted, thick walled bladder with some dilatation of the left ureter (fig. 1, *A*).

The problem arose, what to do! A total cystectomy with excision of the pelvic lymph nodes and diversion of the urinary stream seemed the only possible course of treatment unless we chose to do nothing.

I consulted my radiologist friend, Dr. J. R. Maxfield of Dallas, and he suggested "why not sew some radioactive cobalt in nylon sutures (fig. 1, *B*) into the tumor." As I knew nothing about this modality, he told me that Co_{60} is a pure

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Read before the Johannesburg Clinical and Pathological Club July 14, 1953, and before the Cape Western Branch of the Medical Association of South Africa August 8, 1953.

The radioactive cobalt sutures may be obtained from the Atomic Energy Commission through The Abbott Laboratories, North Chicago, Ill.

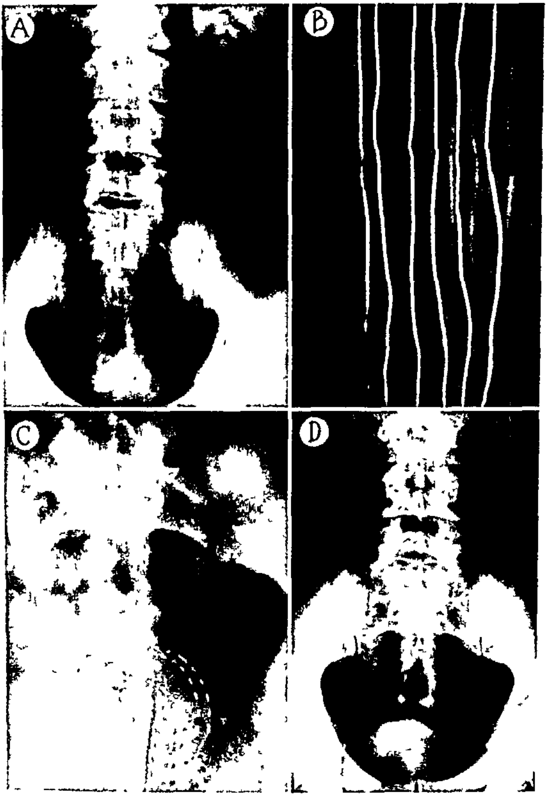

Fig. 1. *A*, preoperative excretion urogram showing small, contracted bladder, dilated distal third of left ureter with retention of dye in pelvis *B*, nylon sutures containing radioactive cobalt (Co_{60}). *C*, cobalt pattern. Note radioactive cobalt in tumor in wall of bladder. *D*, postoperative excretory urogram showing normal sized bladder and good drainage from kidney.

gamma-ray emitter with the result that there is practically no ionization of the tissues and consequently no scar such as one gets with the highly ionizing beta radiation. The Co_{60} can be sewn into the carcinoma, the sutures accurately placed and evenly spaced which permit an almost perfect irradiation pattern (fig. 1, *C*).

As far as we could determine, this material had never before been used in treating carcinoma of the bladder. Consequently as nothing could be lost and much might be gained by the use of such a seemingly ideal modality, the patient was operated on November 20, 1952, and radioactive cobalt was sutured into his carcinoma.

The bladder was opened suprapubically just to the right of the midline and then the left lateral wall of the bladder freed. In this way it was possible to feel as well as see the extent of the tumor. In one area the depth between the bladder mucosa and the outside of the bladder was at least 2 cm. A biopsy was taken from this area. This was later reported to be "a transitional cell carcinoma, grade 3, invading almost completely through the muscularis." Then holding the bladder wall between the thumb and fingers of the left hand, a large needle carrying a nylon suture containing radioactive cobalt was passed lengthwise through the bladder along the outer edge of the palpable tumor. Subsequent sutures were then passed through the wall of the bladder and the carcinoma, each parallel to the other and a centimeter apart. When the entire tumor had been covered in this way, the bladder was closed around a suprapubic tube. Both ends of each nylon suture were brought out through the suprapubic wound (fig. 2, *A*).

The radioactive cobalt sutures were removed November 26, 1952 (fig. 2, *B*) and the patient left for home December 8. January 22, 1953 (6 weeks post-

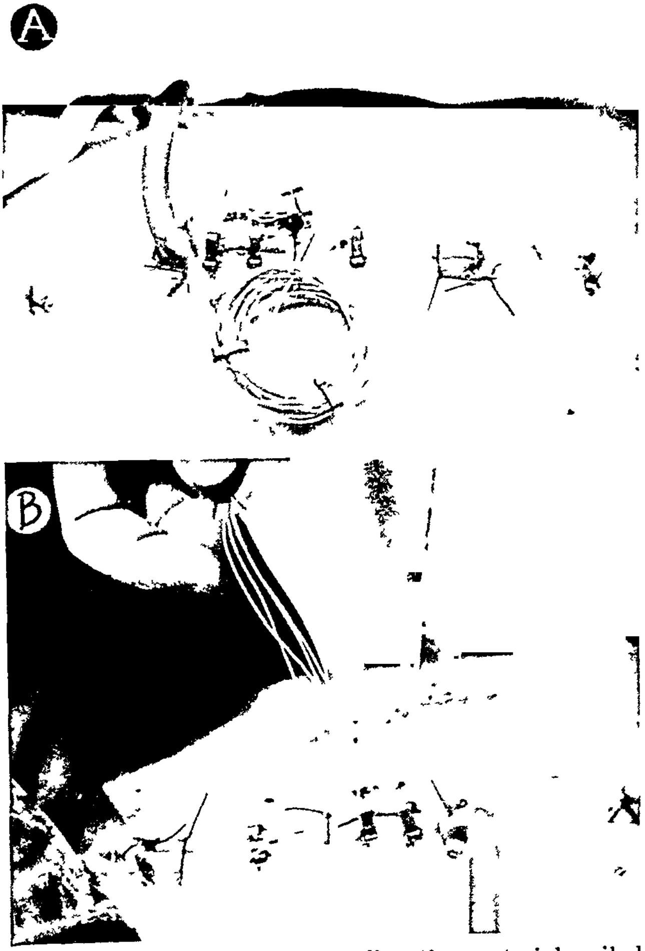

FIG. 2 *A*, note nylon sutures, without any radioactive material, coiled up upon abdominal wall *B*, radioactive cobalt sutures being removed. Radioactive cobalt is visible in suture being withdrawn nearest suprapubic tube.

operatively) he was seen, at which time his bladder capacity has increased from 100 cc to 300 cc (fig. 1, *D*) and except for getting up at night occasionally, he had no urinary symptoms. Cystoscopically, except for some edema in the region of the trigone, the bladder appeared normal. May 4, 1953, almost six months after his operation, it appeared that carcinoma was present over the base of the bladder and trigone. This was one area in which, due to technical difficulties and inexperience, we were not sure that adequate radiation had been obtained. The bladder was re-opened May 14, 1953, and with the aid of Young's boomerang needle, it was possible to sew radioactive cobalt sutures into the region of the internal sphincter and trigone. By the end of June 1953, he was symptomatically well and there was no cystoscopic evidence of carcinoma.

A urinary cripple at the age of 45 due to an extensive, infiltrating carcinoma of the bladder has thus been made a well man symptomatically even though he probably has metastases.

February 4, 1953, a 65 year old man, C. V. V., was referred to me for radioactive gold therapy for an extensive carcinoma of the prostate. He had had two transurethral prostatic resections. The most recent was on January 3, 1953. On rectal examination, the prostate felt very hard, somewhat nodular with extension up into the seminal vesicles, much more so on the left than on the right side. Except for the local extension, there was no evidence of metastasis. On February 5, 1953, he was explored suprapubically. It was seen that he had had a very extensive and adequate resection. There was a large suppurating crater where the prostate had been. The floor of this crater was covered with nodules of actively growing carcinoma. There was not sufficient tissue to permit the injection of radioactive gold with safety so it was decided to sew radioactive cobalt into the prostatic bed (fig. 3). This was satisfactorily accomplished. In June 1953, his doctor wrote me saying "this prostate feels smaller than before he had his

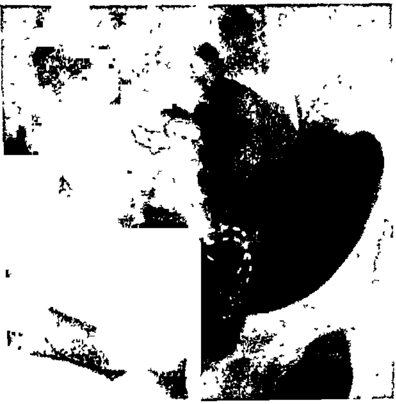

FIG. 3. Radioactive cobalt pattern. Radioactive cobalt is seen in prostatic bed and in region of left seminal vesicle.

radioactive cobalt but there is induration over the posterior half of the rectal vault suggestive of tumor or fibrosis. He is working."

This report is encouraging for it suggests that this may offer another method of intensive local irradiation of the prostate as Young proved was practical many years ago when he used "radium needles."

SUMMARY

For the first time a report is made of a patient with an extensive, infiltrating carcinoma of the bladder which has been satisfactorily controlled with the use of radioactive cobalt in nylon sutures. A good response has also been obtained in using this material in a recently resected extensive carcinoma of the prostate.

ADDENDUM

Since writing this paper and presenting it before the Johannesburg Clinical and Pathological Club and before the Cape Western Branch of the Medical Association of South Africa in July and August, 1953, it has also been presented before the Texas Urological Society in Fort Worth, Texas, in February 1954. To date, five more cases of bladder carcinoma have been similarly treated with equal, if not better, local results. These and other malignant lesions of the genito-urinary tract which we have treated during 1953 and 1954 with radioactive cobalt will be reported later.

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FURTHER EXPERIENCE WITH INTRACAVITARY RADIOCOBALT FOR BLADDER TUMORS

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Five years ago, because of dissatisfaction with previous methods of treatment of bladder tumors, we started to use radioactive cobalt beads for intracavitary irradiation[1] The treatment technique consists of placing the radiocobalt bead in the central channel of a balloon catheter such that when the bag was inflated, the bead was held at the geometric center of the bladder The catheter has special perforations so that it will hold the bead and still permit the outflow of urine

The rationale for using radiocobalt in preference to radium was that the radiocobalt bead, 0 5 cm in diameter, *presents practically a point source of radiation* From such a source, ionizing radiation can be delivered uniformly to the mucosal surface of the spherical bladder as well as, in adequate quantities, into its walls

In the preliminary report in June 1951, we presented the results on 13 patients treated in this manner Since then, 22 additional patients have been treated Some of these patients received external x-ray treatment to the bladder and the perivesical tissues in addition to the intracavitary irradiation with radiocobalt, in order to deliver more adequate doses to the perivesical tissues farther away from the bladder wall

CLASSIFICATION

Lesions have been classified according to anatomical extent as judged by cystoscopic examination and bimanual palpation Jewett's grouping[2] has been followed Group A, tumor confined to mucosa, group B-1, tumor infiltrating but not through more than half the thickness of the muscle, group B-2, tumor infiltrating more than half the thickness of the muscle, group C, tumor extending beyond the bladder wall

It is realized that any anatomical classification based on cystoscopic findings even with bimanual palpation, is subject to error Nonetheless, it can serve as a useful guide in grouping patients Ten patients had lesions classified as Jewett's group A and B-1 Twenty-two patients had infiltrating tumors classified as group B 2 and C Eighteen of these patients had previous treatment, 16 had surgical treatment, and two had surgery and x-ray therapy Only 4 patients in this group had radiation therapy as the primary treatment

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Read at annual meeting, Western Section of American Urological Association, Victoria, B C April 19 22 1954

[1] Schulte John W , Hinman, Frank, Jr and Low Beer, B V A Radiocobalt in the treatment of bladder tumors J Urol , 67: 916, 1952

[2] Jewett, H J and Strong G H Infiltrating carcinoma of the bladder, relation of depth of penetration of the bladder wall to incidence of local extension and metastases J Urol , 55 366, 1946

INTENT OF THERAPY IN RELATION TO DOSAGE

Before subjecting patients to radiation treatment, the intent of therapy was decided upon, that is, eradication, arrest, or palliation. It is our policy in radiation therapy to correlate the intensity of the planned radiation therapy with the goal of the treatment. We believe that when the clinical findings are such that the probability of eradicating a lesion by irradiation is great, then the most intensive treatment within the limits of safety should be carried out.

This grouping of the intent of treatment into eradication, arrest, and palliation appears logical because of the wide dosage range (from 300 r to 8000 r) that is employed in the treatment of a malignant lesion, and is valid, in our opinion, not only for bladder tumors, but malignant tumors of other origin also. Furthermore, such grouping facilitates better evaluation of treatment results with reference to treatment dose. Finally, it provides information whether a lesion was considered at the outset of radiation treatment as "curable" or clinically "incurable".

For carcinoma of the bladder, we believe that adequate eradicative dose may be in the range of 7000 to 8000 r tissue dose delivered in a period of 50 to 60 days. However, when the stage of the disease or the patient's condition makes the probability of eradication remote, then a radiation dose adequate to arrest the rate of the growth temporarily is our aim. We believe that for transitional cell carcinoma of the bladder, the treatment should aim at the delivery of approximately 3000 r to 4500 r in a period of about 40 days. When the lesion is spread beyond the walls of the bladder and/or distant metastases are present, then radiation treatment should aim only to check some of the distressing clinical symptoms, such as bleeding, inflammation, edema and pain. In our experience, a palliative beneficial effect may be achieved with doses varying between 300 r to a maximum of 1500 r tissue dose, given in a period of from 1 week (for 300 r) to 3 weeks.

When eradication or arrest is the goal of treatment, certain more or less severe untoward effects of radiation must be anticipated. Such reactions are unavoidable sequelae of any intensive radiation therapy. When palliation is the goal, then one should limit the dose in order to carefully avoid untoward effects.

RADIATION DATA

Treatment doses are expressed, irrespective of whether the radiation source is radiocobalt or x-rays, in tissue doses, that is, in terms of the dose received by the bladder wall and/or the perivesical tissues. The dose from radiocobalt is estimated at the mucosal surface and at 1 cm. depth. The x-ray treatment dose is estimated as a central beam dose at the level of the bladder or the midplane of the abdomen. With the technique used by us, the difference, whether the calculation is made at the midplane of the abdomen or at the level of the bladder, is insignificant. The treatment dose of radiocobalt varied between 2500 r to 3000 r (twice at 7 to 10 day intervals; total dose 5000 r to 6000 r), and the x-ray dose was around 3500 r in 35 to 40 days. X-rays of 0.95 mm. copper half-value layer or 2.5 mm. copper half-value layer were used in the treatment of these patients.

In the group of patients reported previously, radioactive cobalt beads of approximately 20 millicurie equivalent were used. In the subsequent group, radiocobalt beads of 80 and 90 millicurie equivalent were employed. While the exposure time in the first group of patients was necessarily around 100 hours, the group treated with the high intensity beads had only eight to ten hours. Because of the high dose rate the treatment was not given in one session, but usually in two sessions, one week to ten days apart. X-ray treatment was started immediately after the intracavitary radiation with radiocobalt was completed. In some instances it was started immediately after the first session of radiocobalt treatment and either interrupted for one or two days at the second radiocobalt session, or continued without interruption. In retrospect we feel that many of the severe reactions could have been avoided by greater fractionation and prolongation of the whole treatment over a longer over-all time.

The x-ray treatment was given through four treatment fields. Two 10 by 10 cm. size fields over the lower abdomen and two similar size fields over the opposing sacrogluteal region, i.e., the so-called "cross-fire" technique was followed. The treatment ports were separated in such a way that the medial edges of the treatment beams crossed in the estimated center of the bladder. This was achieved by estimating the position of the bladder from the anterior abdominal wall and from the sacrogluteal surface for patients of various diameters. Desjardin's Cross Section Anatomy was used as a guide. A table for field separation (table 1) was prepared, based on the following calculations: S = DW/tsd, where D = estimated depth of center of the bladder minus 1 cm., W = width of the treatment field, and tsd = tube focus to skin distance.

TABLE 1

Anterior field separation

t cm	d cm	s cm
16	4.5	0.5
17	4.75	0.54
18	5.0	0.57
19	5.3	0.62
20	5.6	0.66
21	5.9	0.70
22	6.2	0.73

Posterior field separation

t cm	d cm	s cm
16	11.5	1.5
17	12.2	1.6
18	13.0	1.71
19	13.7	1.82
20	14.4	1.91
21	15.1	2.02
22	15.8	2.12

In order to have the overlap of the anterior beams occur 1.0 cm. anterior to the center of the bladder and that of the posterior beams 1.0 cm. posterior to the center, it is necessary to subtract 1.0 cm. from the values for the center of the bladder. The table for field separation was calculated on this basis, for t = thickness of patient at level of bladder, and d = depth of bladder.

CLINICAL RESULTS

Of the 35 patients treated up to December 1953, complete follow-up is available in 32 patients. The results are summarized in table 2. Twenty-five patients received intracavitary radiocobalt alone. Ten patients received combined radiocobalt and x-ray therapy. In two patients from this latter group, x-ray treatment was incomplete because the patients' condition did not allow completion of x-ray treatment.

All of the 10 patients with lesions classified as in group A and B-1 were treated with intent of eradication. Five of these patients had surgical treatment prior to radiation therapy, consisting of multiple fulgurations or electrodissection. Only nine of these received the planned dose of radiation. Four of the 9 patients have been free of disease up to 4 years since treatment and are free of disease at this writing. In 2 patients new lesions developed in the bladder, one after 1 year and one after 4 years of radiation therapy. These were subsequently treated by transurethral resection. Three patients had persistent lesions following radiation therapy. One patient did not complete the planned treatment and received only an "arresting" dose with radiocobalt. This patient's lesions first regressed completely but recurred.

TABLE 2

	Noninfiltrating (10 cases)	Infiltrating (22 cases)
"Adequate" treatment	9	14
arrested without recurrences	4	3
arrested with recurrences	2	0
known cancer present	2	1
dead of cancer	1	10
"Inadequate" treatment	1	8
arrested without recurrences	0	0
arrested with recurrences	1	0
known cancer present	0	3
down hill or dead	0	5
Complications		
no significant bladder symptoms	2	0
irradiation cystitis only	4	3
contracted bladder	3	5
"pyobladder", gangrenous cystitis, transplants	1	10
complications not recorded	0	4

In 2 patients of this group no significant bladder symptoms have developed following radiation treatment. In 4 patients mild transient cystitis, in 3 patients contracted bladder, and in 1 patient gangrenous cystitis necessitating ureteral transplantation developed as a sequence of radiation treatment. The radiation cystitis in some cases has persisted for 5 years. In these patients there is seen cystoscopically, atrophy of the mucosa with pale mucous membranes and there are visible areas of telangiectasis.

Of the 22 patients classified in group B-2 and C, 14 were treated with the intent of eradication. Three of these patients have been free of disease for 12 to 23 months. Of the 11 remaining patients, six showed temporary arrest of their tumors while in 5 patients the tumors persisted after radiation therapy. Ten of these 14 patients died with cancer; one is alive with active disease.

Eight patients in group B-2 and C were treated with the intent of arrest. One of these patients has been free of disease for 14 months following treatment, and another for 12 months. Six patients showed only temporary regression of their tumors, lasting from two to five months. Three of these 22 patients with infiltrating lesions showed no response.

In one patient of group C, combined radiation and surgical treatment was carried out according to plan. Resection was done as soon as the acute radiation reaction subsided, approximately six weeks following intracavitary radiocobalt treatment. The patient's recovery was slow, mainly because of osteitis pubis which developed several weeks after surgical procedure. This patient had a very extensive tumor. Although a moderately contracted bladder developed, he appears to be free of disease 18 months after treatment.

One patient was treated for palliation only. Hemorrhage and pain were controlled in this patient for several months by repeated treatment in small doses at four to six week intervals.

DISCUSSION

We know that neither the number of patients studied is large enough, nor the time of observation long enough for conclusive evaluation of this method of treatment. The observations made, however, permit certain inferences. It is borne out in the study that tumors of the bladder in Jewett's group A and B-1 respond satisfactorily to adequate doses of intracavitary radiation. Only three out of 9 patients in this group did not respond to treatment; in 2 patients new lesions developed, while four have remained free of disease so far.

The radiation dose in this group of patients varied between 5000 r to 7000 r, estimated at the mucosal surface. Thus the dose always was below the treatment doses advocated by other investigators, particularly those who used local irradiation to the open bladder. The doses employed were thus in the range for arrest rather than eradication. We expect, however, that even with higher doses not all lesions will be permanently eradicated. Radiation treatment will not of course prevent the development of new lesions, nor significantly influence the intervening mucosa.[3]

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[3] Melicow, M. M.: Histological study of vesical urothelium intervening between gross neoplasms in total cystectomy. J. Urol., 68: 261, 1952.

It appears that intracavitary radiation treatment for the "noninfiltrating" lesion (A and B-1) is not preferable to surgery when there are only one to three lesions present, not exceeding 2 to 3 mm. in diameter. For multiple lesions radiation treatment should be the primary procedure. Surgery following radiation therapy can be carried out without difficulty within the first three to four months. Later, surgical treatment becomes more difficult because it is followed by impaired wound healing.

The severity of post-irradiation complications is in great part dependent on the fractionation of the doses and the overall time taken for the treatment. These factors could not be fully investigated because of our relatively small number of cases, but we intend to examine them in future cases. Use of radiocobalt beads of 30 to 40 millicurie equivalent intensity and a decrease in each separate dose, and so prolong the duration of the whole treatment to three to four weeks is the technique now under consideration.

Infiltrating lesions, as our observations indicate, cannot be adequately treated with intracavitary irradiation alone, for the reason that the dose required to destroy such a lesion at more than 1 cm. depth necessitates the delivery of an exceedingly high dose to the mucosal surface. This is prohibitive because of the severe radiation reaction which usually ensues. Our observations indicate that the combination of intracavitary radiocobalt with external x-ray treatment may be preferable in these cases. Here again further inquiry into fractionation of dose and prolongation of the duration of treatment are necessary before final conclusions may be drawn. The fact that 3 patients out of 14 in this group of infiltrating tumors showed complete disappearance of the tumor justifies, in our opinion, further trial.

One has to realize that in a considerable number of patients, the extent of the disease is such at the time they are seen by the urologist that temporary "arrest" and not eradication must be the goal of any therapy. Finally, there are patients who present themselves in whom even temporary arrest is beyond our reach, and any moderately intensive treatment causes more distress to the patient than relief. With palliative treatment, bleeding and pain may be checked for weeks or even months. Palliative treatment can be repeated at intervals as necessary in the particular case.

SUMMARY

Intracavitary irradiation with radiocobalt alone or in combination with local x-ray treatment has been used for the treatment of 35 patients with tumors of the bladder in various stages of invasion. The impression is gained that:

Many lesions which are not deeply infiltrating can be successfully destroyed with intracavitary radiocobalt irradiation.

In multiple noninfiltrating tumors, intracavitary radiation therapy should not be delayed, but considered as the first method of treatment.

Most of the infiltrating lesions are only temporarily arrested even with combined intracavitary and external irradiation.

Considerable numbers of patients develop varying degrees of radiation cystitis and bladder contraction from the treatment.

Further experience with modifications of the radiation technique, particularly with greater fractionation and prolongation of treatment time, is needed, to attempt to decrease the untoward damage to the bladder in otherwise successfully treated patients.

Radiation treatment in far advanced cases can have a palliative effect only, and may be effective for persistent bleeding.

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THE USE OF RADIOACTIVE GOLD COLLOID IN INOPERABLE CARCINOMA OF THE BLADDER: REPORT OF 2 CASES

CHARLES M. NELSON AND GEORGE Z. WILLIAMS

The problem facing the therapist who is dealing with inoperable carcinoma is the selection of the agent which is capable of producing the greatest radiation damage to a tumor with the least injury to the host. With the advent of radioactive isotopes which became available to us in 1947,* it seemed possible that a valuable tool had been placed in our hands. Clinical evaluation began with its use in inoperable cases, two of which are herewith reported.

Of the isotopes available we chose radioactive gold colloid for the following reasons: 1) It is a solution and can be more readily dispersed throughout a tumor than can seeds or needles. 2) It has a half life of 2.7 days which means that at the end of 9 days all significant external radiation has ceased. There is no further hazard to personnel, and decontamination of dressings, waste, etc. is no longer necessary. 3) Beta emanations comprise 95 per cent of the energy given off. These are trapped by a layer of tissue only ½ cm. in thickness, and the danger to neighboring organs is thereby lessened. The remaining 5 per cent of gamma emanation is an excellent tag for indicating the location of the gold and the amount lost from the area of injection to other organs such as the liver and spleen. This can be done by direct assay with monitoring instruments. 4) We know from the work of Goldie et al.[1] that the emanations will destroy carcinoma cells in experimental animals. 5) We know from the work of Flocks et al.[2] that they will destroy cancer cells in the human. 6) Because of the lessened danger to surrounding structures, very large irradiation doses can be given to the area treated. The unit of dosage is the roentgen equivalent physical or rep. One rep is equivalent to one roentgen as measured by the ionization of matter. One rep produces the same effect as one r of x-ray absorbed. Experimental evidence with biological material indicates that absorption by living tissue of the equivalent ionizing energy produces identical effects.

The disadvantages of the gold colloid are those of any radioactive material with its necessary precautions with regard to personnel plus the difficulty of being certain that all of the tumor is being treated. With a therapeutic effective distance of only 5 mm. it is necessary that the gold be dispersed throughout the tumor in such a way that no area more than 1 cm. in diameter be left uninjected. In a large area this obviously presents technical difficulties. The use of hyaluroni-

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* The radioactive gold used for treating these patients was supplied in part by the Isotopes Branch of the Atomic Energy Commission. This investigation was supported by an institutional grant from the American Cancer Society, and the assay equipment was provided by the Samis Grotto Cancer Research Fund of Richmond, Va.

[1] Goldie, H., West, H. D., Jeffries, B. R. and Butler, C. H.: Proc. Soc. Exper. Biol. & Med., 80: 327–331, 1952.

[2] Flocks, R. H., et al: Treatment of carcinoma of the prostate by interstitial irradiation with radioactive colloidal gold. J. Urol. 68: 510–522, 1952.

dase as a dispersing agent was not helpful in experimental animals,[3] and was not used in our cases

The first case to be reported is a 56 year old white man who was admitted to the Medical College of Virginia Hospital on January 2, 1952 He was complaining of "bladder trouble" of 2 years' duration Frequency and dysuria had become progressively more severe, and finally hematuria became prominent At the time of admission, he was voiding painfully every fifteen minutes day and night

About three weeks prior to admission he had been seen for the first time by Dr John McCusky, of Clarksburg, W Va Following cystoscopy, a diagnosis of infiltrating carcinoma was made, and he was referred to the Medical College of Virginia Hospital for further evaluation and definitive treatment

In addition to his bladder difficulties, the patient complained of shortness of breath on exertion of 10 years' duration, and also of a persistent nonproductive cough He had been hospitalized for a "heart condition" twice in the past 7 years

Physical examination revealed a moderately obese white man propped up in bed His breathing was rasping and his facies had a putty color There was no edema The blood pressure was 130/85 Positive findings were as follows: A markedly emphysematous chest, with breath sounds very distant and rales throughout both lungs, a rounded, somewhat tender mass was present in the right breast, on rectal examination, the prostate was felt to be somewhat enlarged Above the prostate on the right was a firm mass about 3 cm in diameter. The mass was not fixed to the perivesical structures

Blood studies were within normal limits The urine showed 1 plus albumin, 20-30 white blood cells per high power field and innumerable red blood cells

X-rays of the chest, together with confirmatory skin tests, led to the diagnosis of healed histoplasmosis An excretory urogram showed only that both kidneys were functioning On cystoscopy, there was an ulcerated lesion surrounding the right ureteral orifice The orifice could not be distinguished The lesion was elevated, but flat, and was an angry red A biopsy was reported as a squamous cell epithelioma, poorly differentiated (fig 1, *A*)

In view of the poor general condition of the patient and the probability of the spread of the growth beyond the confines of the bladder muscularis, it was felt that with surgery little hope of cure could be entertained It was decided, therefore, to attempt palliation and possible cure by the use of radioactive gold colloid Accordingly, on January 10, 1952, the tumor was exposed suprapubically and 15 millicuries of the colloid in 15 cc of Ringer's solution with 0 3 cc of 1-1000 adrenalin were injected into the tumor, into the bladder around the tumor and into the adventitia of the bladder beyond the tumor total dosage, 1,140,000 rep

The technique of the injection was as follows The colloid was divided into 3 cc aliquots each in a syringe with lumbar puncture needle attached These were kept on a separate table removed from the operating table When the lesion was exposed an open sponge was placed at the internal urethral orifice to absorb any spillage The syringes were passed to the surgeon one at a time, and were handled

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[3] Williams, George Z Unpublished

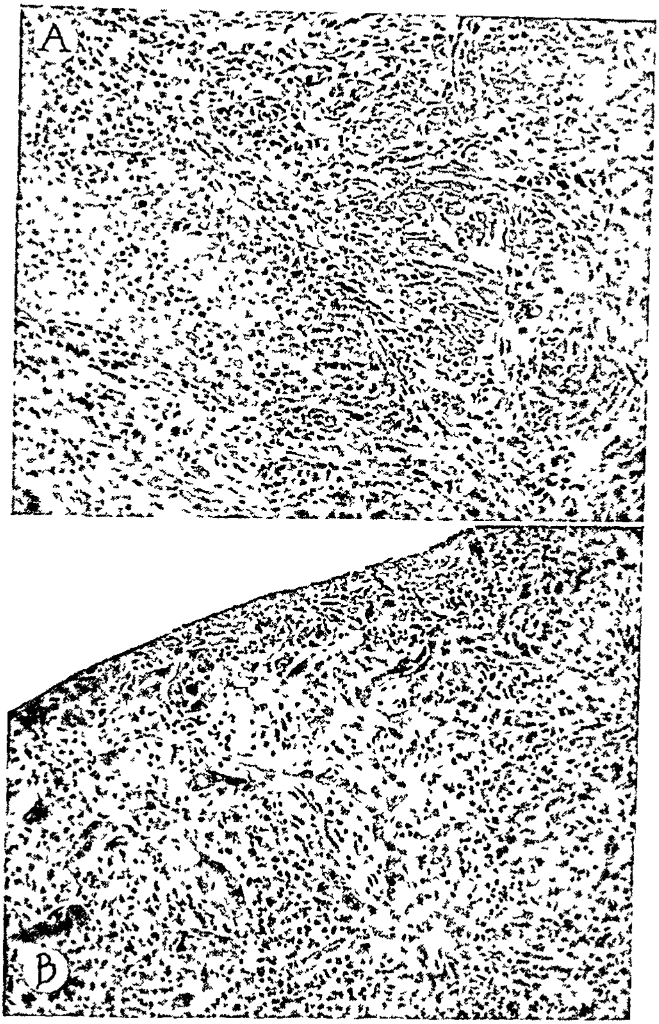

FIG. 1. Case 1. *A*, biopsy of tumor showing extension into muscle bundles. *B*, biopsy 2 months after treatment with Au^{198}. Activity still present, but appearance vastly changed

by the plunger of the syringe in order to stay as far away from the radioactivity as possible. The solution was then injected throughout the tumor, keeping the point of the needle in practically constant motion. After the injection the sponge was removed from the bladder, and the area sponged lightly with another loose sponge. Both of these together with the sponge forceps were placed on the syringe table for decontamination. The surgeon dropped out as soon as the sponges were removed, and the wound was closed by the assistants. The operating time of the surgeon and assistants was clocked by the radioisotope chemist, and the total exposure for each measured. An exposure of 0.1 r was not exceeded. The procedure was of short duration, and there was ample time for Dr. C. L. Coleman to remove the breast tumor. This proved to be gynecomastia.

On his return to his room the patient was isolated in a single room, and nursing care was limited to portions of each hour so that total body exposure of each nurse was less than 0 1 r each day and 0 3 r each week This worked out to fifteen minutes out of each hour for the first two days After irradiation from the body dropped to less than 12 mc per hour at a distance of six inches or less from the treated area, isolation and limitation of nursing care were dispensed with At the end of 7 days no precautions were necessary

The suprapubic catheter was removed on the eighth day, and the urethral catheter on the thirteenth The patient voided at first with discomfort but without suprapubic leakage, and by the seventeenth day he was voiding without burning or urgency Cystoscopy on the nineteenth day disclosed the right orifice projecting up from a crater about 1 cm in diameter. The posterior margin of the crater was reddened, and there was a whitish exudate on this edge He was discharged on the twenty-first postoperative day It was felt that he was much improved

The patient was re admitted 2 months later for check-up cystoscopy During the interval he stated that he had had drainage from his suprapubic wound on several occasions He still had nocturia from one to five times, but neither burning nor urgency His major complaints were cough and shortness of breath Physical examination revealed the same severe emphysema, and a well healed midline abdominal scar On rectal examination, however, a mass about the size of a lemon was readily palpable above and on both sides of the prostate, the base of which comprised a portion of the mass It was not certain whether this represented tumor growth or inflammatory reaction to the gold colloid Cystoscopy revealed an ulcer with a whitish base in the region of the right ureteral orifice The bladder surface around the ulcer was elevated and thrown up in folds A biopsy from the ulcer margin revealed undifferentiated carcinoma of the urinary bladder (fig 1, *B*)

On April 18, 1952, the suprapubic incision was reopened and 18 mc of radioactive gold colloid injected into the tumor and surrounding bladder Technical difficulties were negligible Again the convalescence was all that could have been hoped for, although he complained of burning around the incision for 2 weeks postoperatively, and the incision was slow to heal He was discharged on the twenty first postoperative day in fair condition He was seen again 2 months later at which time he was complaining of frequency and burning on urination, and rectal burning and diarrhea On rectal examination, there was a large, fixed mass involving the base of the prostate and extending above it Cystoscopy by Dr McCusky in Clarksburg indicated that a growth was present in the bladder Proctoscopy showed that the bowel was irritated, but without evidence of new growth From that time until 2 months later in August, when he died, the course was progressively downhill, and pain both from the bladder and rectum became so severe that it was finally uncontrollable even with massive doses of morphine On the day of his death while in the hospital in Fairmont, W Va , he became psychotic and violent, and died apparently of exhaustion

The second case is that of an 88 year old white man who in 1951 had a seg-

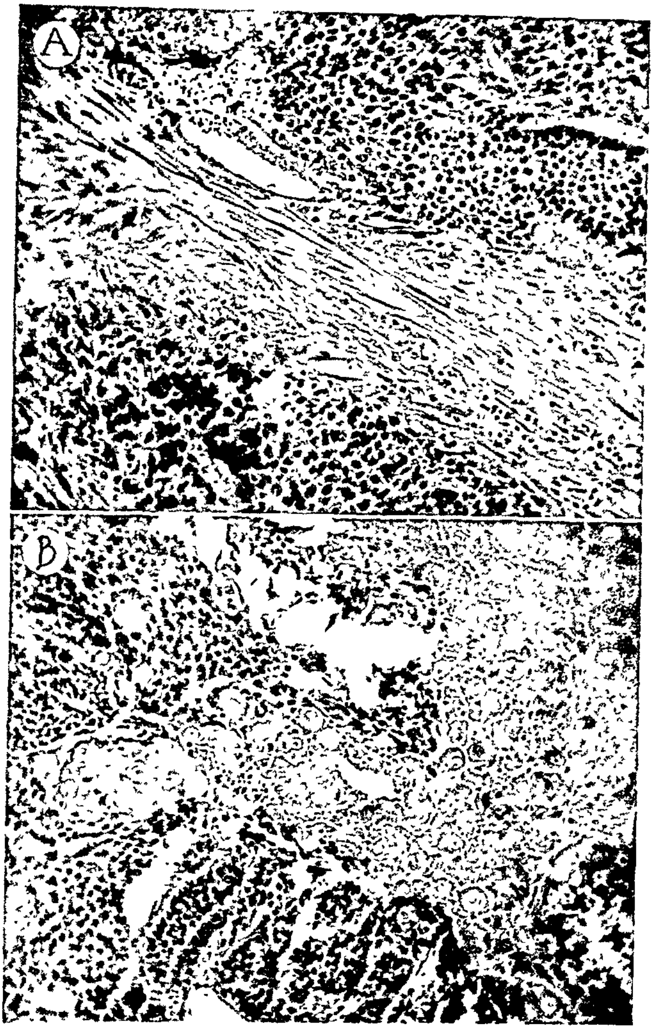

Fig. 2. Case 2. *A*, biopsy of recurrent carcinoma of bladder. *B*, section from recurrence in suprapubic wound.

mental resection of a large bladder tumor. The tumor was in the dome of the bladder at the limit of vision superiorly when using the foroblique lens. The tumor was classified as a squamous cell epithelioma of the bladder (fig. 2, *A*). In addition to the segmental resection, a capsule of 50 mg. of radium was placed within the lumen of a 30 cc balloon catheter, and the balloon inflated with water after the catheter had been passed into the bladder per urethram. This was done on the first postoperative day. The radium was left in the bladder for 18 hours. In addition to this, beginning 3 weeks after the operation, 1000 r of deep x-ray therapy was given through four portals. This had to be discontinued because of the general condition of the patient.

The patient, oddly enough, was made comfortable by these procedures. With the aid of antibiotics his urine became clear, and he got up only once or twice at night, but at the time of his 6 month check-up, a nodule was found in the suprapubic incision. The nodule was superficial and was movable. It was felt that this

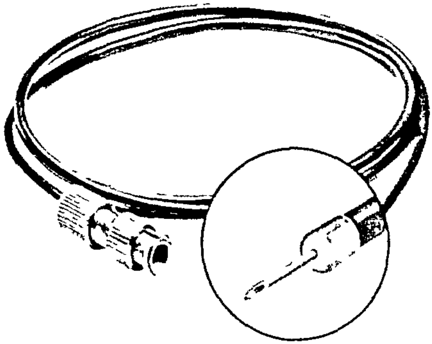

Fig. 3. No. 5 ureteral catheter with No. 22 needle attached.

was a recurrence, and he was re-admitted to the hospital. The nodule was excised *en bloc* with a wide margin of surrounding tissue. It was not necessary to incise the rectus sheath. The pathological report was squamous cell epithelioma (poorly differentiated) of the abdominal wall following squamous cell epithelioma of the bladder (fig. 2, *B*).

Cystoscopy showed a recurrence approximately 1½ cm. in diameter in the dome of the bladder. On May 30, 1952, under spinal anesthesia the No. 21 Brown-Buerger cystoscope was passed, and 10 cc radioactive gold colloid were injected into the tumor. On this occasion the radioactivity of the solution was 2 mc. per cc. The dose given in r equivalents was 1,500,000. The instrument used wa[illegible] No. 5 ureteral catheter with 1 cm. of a No. 22 needle attached to the tip. At t[illegible] point of attachment of the needle was a shoulder which prevented the o[illegible] tion of the needle (fig. 3*). There was no difficulty with the injection. [illegible] needle point was inserted into various portions of the tumor at varying [illegible] and after insertion the colloid was injected by Dr. Williams standing [illegible] operator. Uniform distribution of the gold seemed adequate at the time.

The patient was discharged from the hospital on June 4, 1952, and [illegible] the office on June 11. The urine was clear and he was voiding com[illegible] weeks later a fixed mass could be felt in the right lower quadrant. Th[illegible] in size from week to week, and his course was steadily downhill. [illegible] in November 1952. During this final stage dysuria was notable [illegible]

DISCUSSION

We embarked on our first case with the object of obtain[illegible] following the first injection, this was achieved; urination w[illegible] still frequent. The finding of active tumor at the time of [illegible] tion led us to inject the area again, and this time the p[illegible] increased and rectal irritation became prominent. The importance of the role played by the gold, by the growth, and by antibiotic reaction in causing his pain could not be evaluated, but each was felt to be a factor. In the second case we felt that we achieved real palliation. The patient died of widespread metastasis, but with little or no discomfort on urination.

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* The device was constructed by Mr. Outwin, of C. R. Bard [illegible]

Although there is little to show for our efforts in these two cases, it is our belief that radioactive gold colloid is a therapeutic agent which, when thoroughly evaluated, will assume a useful role in the treatment of bladder tumors.

SUMMARY

Two cases of inoperable carcinoma of the bladder treated by radioactive gold colloid have been presented.

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POLYPOID FIBROMYXOSARCOMA OF THE URINARY BLADDER IN A CHILD

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Polypoid fibromyxosarcoma of the urinary bladder is a rare disease. The material to be presented has already been reported by Mostofi and Morse* in a group of 10 cases collected by the Army Institute of Pathology. However, the complete details were not presented, and since the total number of cases is extremely small, all the facts from each observed case should be recorded so that the life history and course of this disease can be understood. In addition, this patient has survived for 8 years and, as far as we can determine, is the only one to survive more than 24 months.

There has been considerable confusion in the classification and terminology of this disease which stems from the fact that several types of cells may be present. Histologically, these tumors may be composed of loosely arranged, round cells; elongated cells with centrally placed nuclei, longitudinal fibrillae, and cross striations; and vacuolated, multinucleated giant cells. While all three of these cell types have been observed, they need not be present in all tumors.

The neoplasm is thought to arise from embryonic tissue which is capable of differentiation into myxomatous, fibrous, or muscular cells and may account for the varied histological picture. Some of the tumors contain a much greater component of myxomatous elements than others, producing a polypoid gross appearance. Because of this histological confusion, the term "sarcoma botryoides" has been used to describe these tumors. Actually, this is a poor term since it only denotes a neoplasm arising from mesenchyme which has a grape-like appearance. Therefore, it may be best to simply classify these tumors by the type of cells present until further light has been spread upon their embryogenesis.

CASE REPORT

J. S., No. 46-7796. On July 16, 1946, a 5-year-old white boy entered the Urology Department of University Hospitals with a 7-week history of straining on urination, hematuria, and passage of small pieces of tissue and clots. Four weeks prior to admission he was unable to void and was catheterized by the family physician. After that incident he had marked frequency and nocturia.

Physical examination revealed a well-developed, well-nourished, white male child in no acute distress. Aside from a slight enlargement of a few cervical lymph nodes, the head and neck were normal. The lungs were clear to percussion and auscultation. There was a systolic murmur over the mitral and pulmonic areas. No masses or organs were palpable in the abdomen. Rectal examination revealed no abnormalities. The extremities were normal.

At the time of admission the hemoglobin was 11.7 gm., a red blood count 4,100,000 and a white blood count 30,900. A urine analysis revealed a pH of

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* Journal of Urology 67: 681–687, 1952.

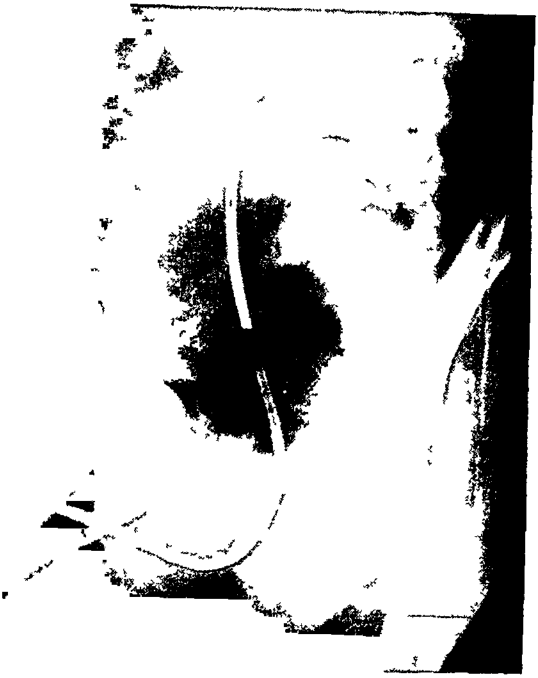

FIG. 1. Air cystogram in oblique position demonstrates filling defect arising from posterior inferior wall of bladder and protruding intravesically.

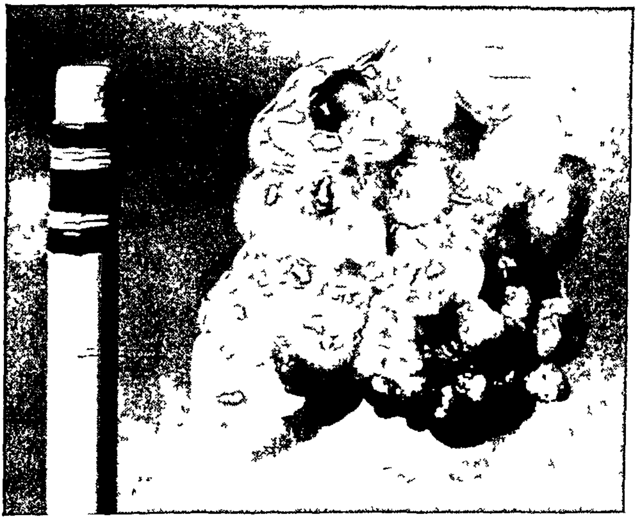

FIG 2. Polypoid mass of intravesical neoplasm removed suprapubically

7.0, specific gravity of 1.015, negative albumin and sugar reaction with 40–50 red blood cells, and 4–5 white blood cells per high power microscopic field. The blood urea nitrogen was 14 mg. per cent and the creatinine 1.2 mg. per cent.

Opaque and air cystograms revealed the bladder to be of normal size with a polypoid filling defect located inferiorly and posteriorly just to the left of the midline (fig. 1). A chest x-ray was normal.

The day following admission a cystoscopic examination under general anesthesia was performed, and the filling defect noted on the cystogram was identified

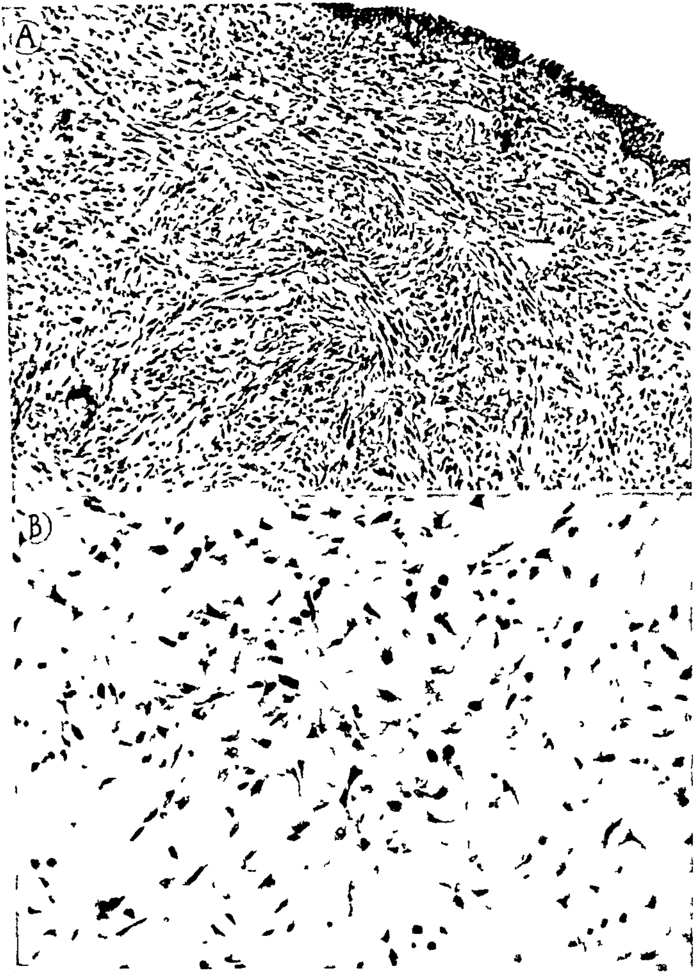

Fig 3 *A*, photomicrograph of polypoid intravesical neoplasm *B*, high power view exhibits cellular structure of polypoid intravesical neoplasm

as a mass of polypoid neoplasm arising from the bladder neck The remainder of the bladder appeared normal On July 19, 1946, the bladder was exposed suprapubically, and, when it was opened, the neoplasm looked like a bunch of grapes lying in the bladder The neoplasm was resected flush with the bladder, and the base, which was located within the internal urethral orifice, was thoroughly coagulated with the high frequency current.

The gross pathological specimen consisted of twenty grams of polypoid masses of soft, pale, transluscent tissue with many globular masses measuring 0.5 to 2 cc in diameter, covered with a smooth, glistening epithelium and filled with a pale, transluscent, jelly-like substance (fig. 2). The microscopic sections showed a highly vascular, loose connective tissue resembling embryonic mesenchyme with an investing layer of normal appearing transitional cell epithelium (fig. 3, *A*). Cellular elements consisted of thinly spaced cells with large, richly chromatic ovoid, spindle-shaped, or stellate nuclei. The cytoplasm was abundant, stained faintly basophilic, and formed a network of fibrillar intercellular processes (fig. 3, *B*). Mitotic figures were fairly numerous. In several areas there was hemorrhage, necrosis, and infiltration by chronic inflammatory cells. Clusters of very large, monocellular cells with vacuolated cytoplasm were seen in several areas. The pathological diagnosis was fibromyxosarcoma of the bladder.

The child made an uneventful recovery and was discharged on August 17, 1946, with the suprapubic incision completely healed.

Following discharge, the urethral stream gradually became smaller and difficult to start. Three weeks prior to re-admission he began complaining of severe suprapubic burning each time he voided. The family physician felt that bladder neck obstruction had recurred, and the incision in the bladder had re-opened. He made a small suprapubic skin incision, re-establishing the suprapubic sinus. On October 25, 1946, the patient was re-admitted to the hospital voiding partially

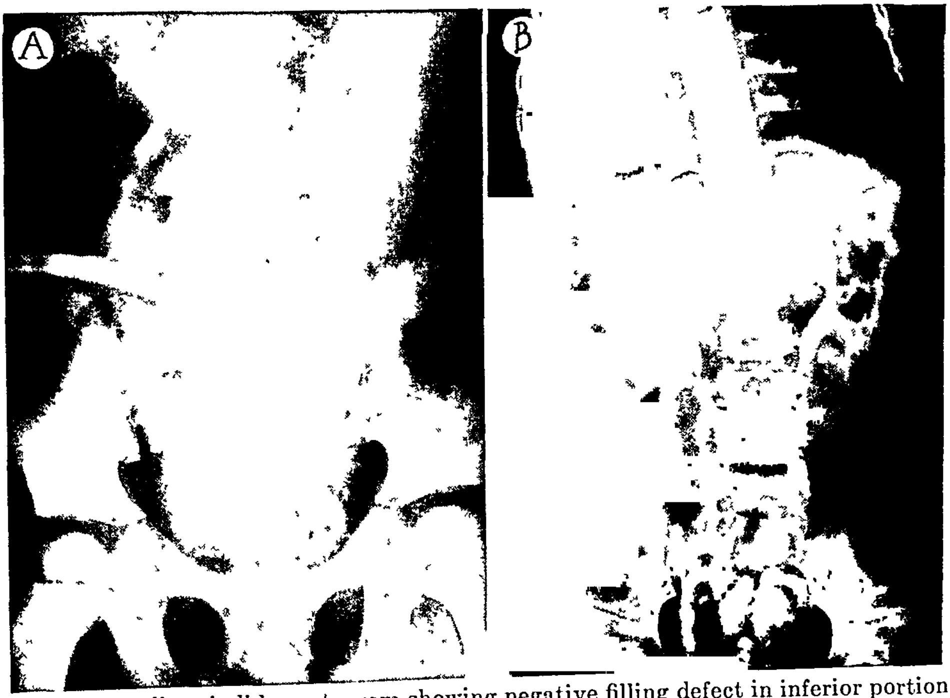

FIG. 4. *A*, sodium iodide cystogram showing negative filling defect in inferior portion of bladder representing regrowth of polypoid neoplasm. *B*, excretory urogram reveals mild bilateral hydro-ureters.

through the urethra, but leaking the major portion of urine through the suprapubic wound. A cystoscopic examination was performed through the suprapubic sinus, and recurrent neoplasm was found arising from the bladder neck, obstructing the internal urethral orifice. A repeat opaque cystogram revealed a filling defect in the inferior half of the urinary bladder which was irregular and ragged in outline (fig. 4, *A*). An intravenous urogram revealed a mild bilateral hydroureter (fig. 4, *B*).

Because of the rapid growth of the neoplasm and recurrence of bladder neck obstruction, additional therapy was recommended. Since this type of neoplasm is radio-resistant, cystectomy and uretero-intestinal anastomosis were advised. On November 30, 1946, a bilateral uretero-intestinal anastomosis was performed. When the abdomen was opened, the bladder was noted to be three times normal size and full of tumor. A small extravesical nodule was noted and removed. The pathological report was chronic hyperplastic lymphadenitis with granulomatous changes. Both ureters were slightly dilated but otherwise appeared normal. A side-to-side anastomosis with an intact ureter was performed. Ureteral catheters were used as splints and allowed to exit through the anus. The child responded well postoperatively, and 10 days later the lower segment of the intact ureter was ligated. The patient continued to improve, and on December 27, 1946, a total cystectomy was performed. There was no evidence of local spread or metastases to the regional lymph nodes.

The gross pathological specimen consisted of a bladder in which a large, polypoid, myxomatous tumor mass was growing out of the posterior wall and filling

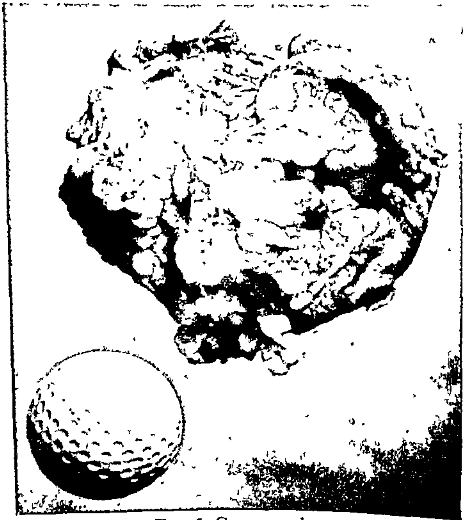

FIG. 5. Gross specimen

the bladder lumen (fig. 5). The specimen weighed 120 gm. The tumor tissue was soft, friable, myxomatous, and marked by interstitial hemorrhage. On cut section the neoplastic tissue appeared to be invading the bladder wall, but the serosal surface was not involved by the neoplasm.

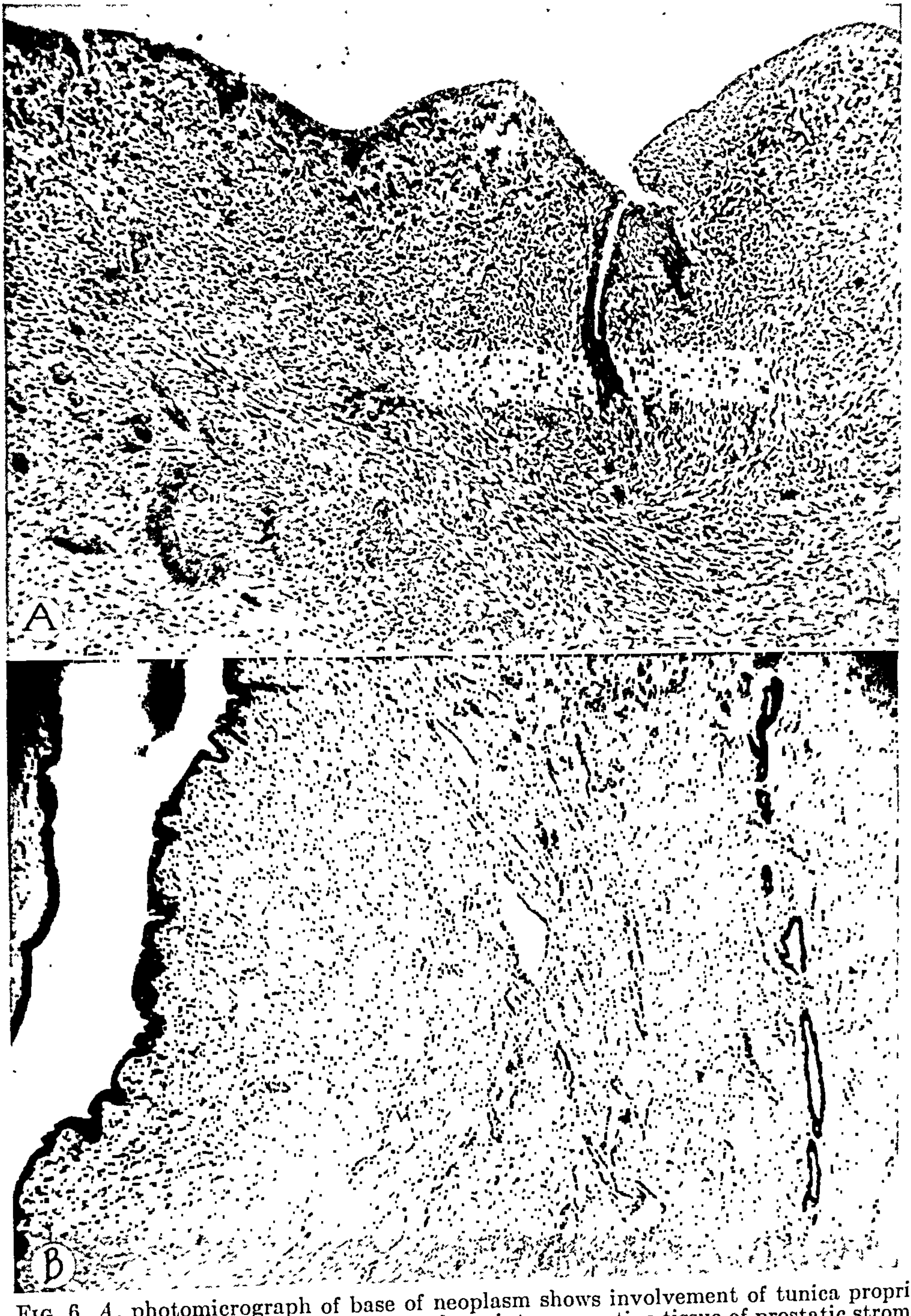

FIG. 6. *A*, photomicrograph of base of neoplasm shows involvement of tunica propria. *B*, prostatic urethra with extension of neoplasm into connective tissue of prostatic stroma.

The microscopic sections showed the neoplastic tissue to consist of a vascular, loose, connective tissue. The neoplastic cells were thinly spaced with large, hyperchromatic stellate or spindle-shaped nuclei. There was a moderate amount of cellular basophilic cytoplasm which formed a very light network of fibrillar intercellular processes. The polypoid processes were covered by a layer of essentially normal-appearing transitional epithelium. The anaplastic cells were seen to be growing freely from the connective tissue of the bladder tunica propria (fig. 6, *A*). No invasion of the muscularis was noted. Sections of the prostatic urethra and prostate showed the neoplastic, myxomatous connective tissue to be continuous with the connective tissue of the prostatic stroma (fig. 6, *B*). The pathological diagnosis was fibromyxosarcoma of the bladder, prostatic urethra, and prostate.

The child made an uneventful recovery and was discharged from the hospital on January 16, 1947. He was passing his urine freely through the rectum, and a postoperative intravenous urogram revealed a normal right pyelogram and mild hydronephrosis on the left (fig. 7).

Throughout 1947 repeated examinations were performed in the out-patient department. The child gained weight, played vigorously, and had no complaints. Several chest x-rays were normal, and repeated intravenous urograms revealed mild left hydronephrosis. The last contact with the patient was on October 16, 1953, at which time he was 13 years of age, attending school regularly, and joining in normal activities.

Sections of the tumor were examined by the Army Institute of Pathology, and

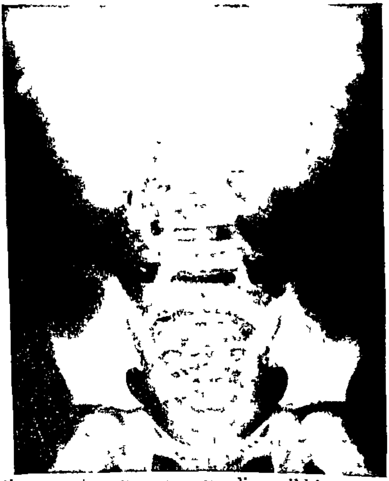

FIG. 7. Postoperative excretory urogram revealing mild left hydro-ureter and hydronephrosis.

their impression was: "Accession No. 235129: Your case has aroused considerable interest. The staff believes that the tumor is analogous to sarcoma botryoides in the vagina of children."

CONCLUSION

The case history of a very interesting and rare bladder neoplasm found in a 5-year-old boy has been presented. The neoplasm arose from the region of the internal urethral orifice and was classified as a fibromyxosarcoma. Treatment consisted of suprapubic excisions and fulguration of the base of the neoplasm, but was rapidly followed by recurrence of the growth and bladder neck obstruction. The final definitive therapy consisted of uretero-intestinal anastomosis and total cystectomy. The child has now survived 8 years.

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CARCINOMA OF THE BLADDER IN CHILDREN CASE REPORT

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Carcinoma of the bladder in the first decade of life is exceedingly rare Prior to 1937 the literature contained one case, reported by Deming in 1924 In 1949 the Carcinoma Registry of the American Urological Association contained only 2 cases In 1951 the Armed Forces Institute of Pathology reports 1 case in 6,000 is below the age of 12, an 11-year old child A review of cancer in children by Dargeon in 1948 does not mention cancer of the bladder It is our belief that the literature is without a detailed case report and only 4 cases have been mentioned by reference only The rarity of this tumor in children, and reports thereon, prompted us to add our case, which we believe is the fifth case in the literature

CASE REPORT

On September 9, 1953 a 6-year old boy called his mother to the bathroom and pointed out a "commode full" of bright red blood He had no complaints, nor had he been ill At this time his mother discovered that his urinary stream would often stop suddenly and start again He was seen by his physician, and penicillin 300,000 units daily for 6 days was given At the end of this time he was still passing blood intermittently, painlessly, more marked at the end of urination He was hospitalized locally for a week and transferred to us for evaluation During the entire period gross or microscopic blood was constantly present in the urine

The patient had had measles, mumps and chickenpox There was no history of scarlet fever, urinary tract infection, nephritis, injuries or operations The child did not have enuresis

The child was well developed and well nourished Temperature 98 degrees, pulse and respiration normal Examination externally was normal except for a vague, small mass one inch in diameter in the left suprapubic region It was movable and slightly tender

All laboratory studies showed nothing remarkable Urinalysis grossly pink, 1 025 specific gravity, albumin 4 plus, sugar negative, microscopic loaded with red blood cells, no casts, culture no growth

On October 1, 1953, under general anesthesia, a 15F cystoscope was introduced without difficulty No abnormality was noted except the tumor, described as follows There was a stalk about three centimeters in length attached to the dome of the bladder, slightly to the left, and somewhat anterior in position At the distal end there was a large tumor shaped like an inverted umbrella, with the fronds pointing distally In the center was an ulcerated area which had been bleeding (fig 1, *A*) The tumor was edematous, red, with some inflammatory reaction As the bladder was emptied it was easily observed how the fronds of

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tumor through the cystoscope was much more formidable than the microscopic sections. Treatment of these lesions is by segmental resection suprapubically, or electroresection, either transurethrally or suprapubically. The age of this patient and easy accessibility of the tumor made segmental resection the treatment of choice.

SUMMARY

A case of papillary carcinoma of the bladder, grade 1, in a 6-year old boy is presented. We believe this to be the fifth case mentioned in the literature under age 12. The evidence in this case indicates that the tumor certainly developed long after birth, that is, it was not congenital. Treatment consisted of a segmental resection of the whole thickness of the bladder wall at the attachment of the tumor with a margin of one and one-half centimeters wide of the stalk. The patient was well, with a normal bladder capacity 4 months after operation.

ADDENDUM

The patient is well with a normal bladder 14 months after operation.

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MITOTIC ACTIVITY OF EPITHELIUM OF URINARY BLADDER IN ALBINO RAT

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Mitotic cell divisions have been described as occurring in the deep and not in the superficial layers of the bladder epithelium in the rat[1-3] and in other species.[4-6] Furthermore, it was postulated that, as in stratified epithelia, the cells arising by mitosis in the deep layers would migrate toward the surface, transform into the characteristic cells of the superficial layer and eventually be lost by desquamation into the lumen of the bladder.[2-6] To test this hypothesis, the mitotic activity of the transitional epithelium was investigated in animals treated with colchicine—a substance which prevents dividing cells from progressing beyond the metaphase stage and thus leads to the accumulation of arrested metaphases in areas of mitotic activity.[7] For this, 48 male Sherman rats weighing 164–214 gm. were divided into four groups of 12 animals each, all of which were injected with a single dose of colchicine (0.1 mg. per 100 gm. body weight). These four groups were injected respectively at 7 a.m., 12 noon, 7 p.m. and 12 midnight. Each group was divided into three subgroups the animals of which were sacrificed at exactly 2, 3 and 4 hours after colchicine administration. The bladders were fixed in Susa and the sections stained with Masson's trichrome.

Examination of the histological sections showed that the epithelium of the urinary bladder in the rat is composed of surface and deep layers. The *surface layer* is made up of a single cellular row in contact with the lumen; the cells are large, often binucleated, and are referred to hereafter as "surface cells." The *deep layer* is apparently composed of several cellular strata located between the surface layer and the lamina propria; the cells are smaller than those of the surface layer, and are referred to hereafter as "deep cells." By nuclear counts it was found that 9.7 per cent of the nuclei were present in the surface layer and 90.3 per cent in the deep layer.

Mitotic figures were seen in both surface (fig. 1) and deep layers (fig. 2). Since the animals had received colchicine, only prophases and blocked meta-

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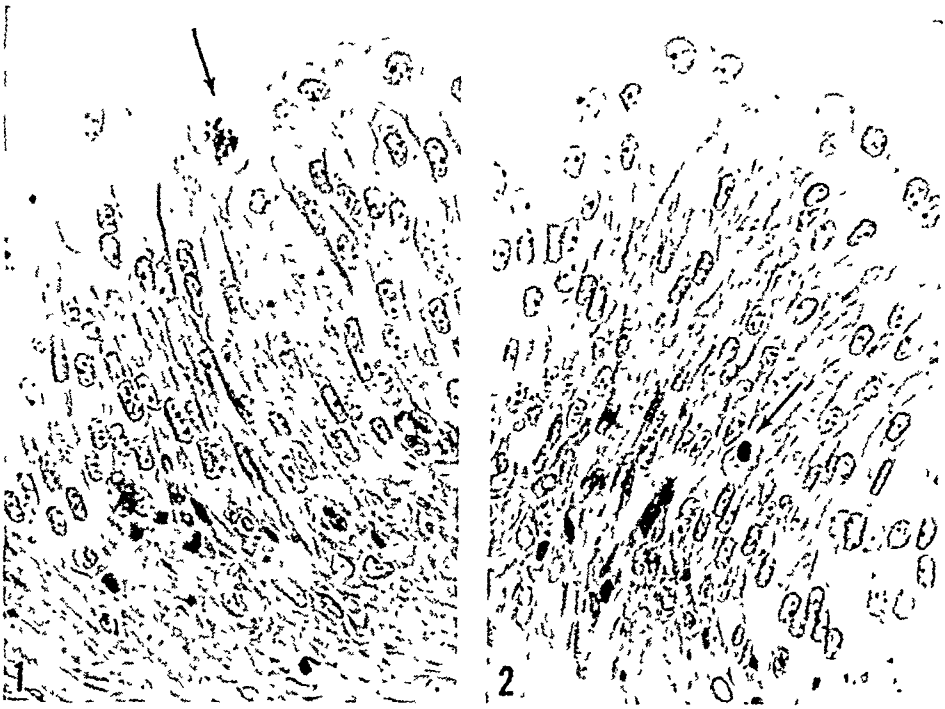

FIGS. 1 and 2

TABLE 1

Time of Injection	Percentage of cells dividing per hour	
	Deep layers	Surface layer
12 noon	0.21	0.27
7 p.m.	0.04	0.10
12 p.m.	0.01	0.08
7 a.m.	0.01	0.06
Grand Average	*0.07*	*0.13*

phases were present. To evaluate the mitotic rate of the two cell types, 2000–2500 nuclei per bladder were counted in fields selected at random in the bladder epithelium. A record was kept of the number of nondividing nuclei and mitoses (prophases and metaphases) for the surface and deep layers. The mean mitotic activity per hour of both cell types was calculated in each subgroup by dividing the number of mitoses observed in any one animal by the number of hours between colchicine injection and sacrifice and averaging these figures (table 1). The number of cells undergoing mitosis over a 24-hour period was calculated to be approximately 1.6 per cent for deep cells and 3.1 per cent for surface cells.

At all the time intervals studied, the mitotic activity of the epithelium was less in the deep than in the surface layer (table 1). In addition, the mitoses of both layers were most numerous in the animals injected at noon and least so in those injected in the early morning, a fact showing that the mitotic activity of the bladder epithelium was subject to diurnal variations.

The high rate of mitotic activity suggested that here, as in other epithelia,[8-10] newly-formed cells may replace those lost by desquamation. Previous authors stated that this loss was compensated by cells arising from mitoses of the deep cells.[1-6] The finding of abundant mitoses in the surface layer indicated that cellular replacement may also be provided by surface cells.

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THE EXPERIMENTAL USE OF SEROMUSCULAR GRAFTS IN BLADDER RECONSTRUCTION: PRELIMINARY REPORT

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A feasible method for the plastic reconstruction, repair, or substitution of congenital or surgically acquired defects in the urinary tract has been long looked for by the urologist. A practical method of accomplishing these objectives would lend itself to the solution of many difficult clinical problems met in the urinary tract. A new method for the plastic reconstruction of the urinary bladder using seromuscular grafts from the terminal ileum and colon is herein described together with our observations regarding the functional capacity and physiologic characteristics of the reconstituted organ.

The repair of defects and reconstruction of the bladder have been attempted by others with a variety of materials. The use of free fascial grafts, segments of intestinal tract, pleura, peritoneum, and gallbladder has been reported. Each method described has had serious drawbacks and none has proved entirely satisfactory clinically.

The use of free fascial grafts, in experimental animals, was reported by Neuhof,[1] Koontz,[2] DeMuth,[3] and Baret.[4] Transitional epithelium from the bladder was found to overgrow the fascial graft. However bone formation and shrinkage of the graft was reported in the majority of cases. Repair of one case of exstropy of the bladder, in man, was reported by Kirscher,[5] with demise too soon for evaluation.

The use of ileal segments to increase bladder capacity has been reported by a number of authors.[6, 7, 8] Cibert[9] reported the use of this technique in a case of contracted bladder resulting from tuberculosis.

The use of the terminal ileum with a portion of the ascending colon, as a

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Note by editor. Drs. Shoemaker and Marucci were awarded a prize in the Essay Competition held annually by the American Urological Association under the Committee on Scientific Research, Dr. Miley B. Wesson, chairman.

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substitute bladder, with preservation of the urethra or an artificial stoma to divert the urinary stream has been reported by a number of authors.[10] [19] Rubin[20] reported on the use of a portion of a sigmoid as an artificial bladder together with an exhaustive survey of the literature

These have appeared to work well in some instances but in all the absorption of urinary constitutents and the persistence of the mucus secreting intestinal epithelium have been serious drawbacks.[21]

Lay[22] used a preserved gallbladder as a substitute bladder, in one human case with postoperative death from uremia

Small defects in the alimentary tract have been repaired with portions of pleura and peritoneum,[23] as patches, with epithelialization However repair of the bladder has not been reported.

The use of intestinal flaps devoid of mucous membrane in the problem of common duct repair was first attempted by Grotzinger, Shoemaker and Zaydon [24]

In approaching the problem of bladder reconstruction it was felt that an ideal tissue graft for segmental repair or complete substitution of the bladder should satisfy the following criteria:

1) The material must be easily available in the form of an intact, viable graft

2) Large areas of the potential graft must be readily available and easily mobilized without jeopardizing the intact blood supply.

3) The graft should be such as to allow the regeneration and regrowth of the transitional type epithelium normally found in the bladder.

4) There should be sufficient pliability of the graft material to allow it to be shaped to the general configuration of the bladder.

5) The graft should have an inherent functioning muscle layer.

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6) The graft should not resorb electrolytes or nitrogenous wastes of the urine.
7) The graft should not produce mucus or irritating substances.

MATERIALS AND METHOD

Six male and four female mongrel dogs weighing from ten to sixteen kilograms form the basis of this report. Under intravenous nembutal (60 mg. per 5 kilograms body weight as an initial dose) and pentothal anesthesia, a loop of terminal ileum or colon approximately ten to twenty centimeters in length was served from the intestinal tract. The continuity of the gastro-intestinal tract was reconstituted by means of an end-to-end anastomosis.

A longitudinal incision through the bowel wall of the isolated loop was made approximately one-half to one centimeter from the mesenteric border. The mucous membrane was elevated and completely removed from the muscular layers. The flap was then folded transversely with the serosal surfaces facing each other; the two leaves were united by means of a continuous suture placed one-half to one centimeter from the mesenteric border on the opposite side of the mesentery as the previously described longitudinal incision. Thus a "hod"-shaped seromuscular flap with a mesenteric pedicle was created. Approximately ninety per cent of the bladder was resected, leaving only the trigone and a narrow margin of residual vesical tissue around the urethra and ureteral orifices. The graft was brought inferiorly to the region of the bladder and vesical remnant. A No. 14 dePezzer catheter was inserted through the anterior wall of the newly reconstructed bladder and brought out through a separate stab wound in the skin. The abdominal wall was closed in layers.

Excretory urograms, cystograms, and cystometrograms were done under very light anesthesia of intravenous pentothal for better control in the handling of the dogs. Urograms were made with 70 per cent urokon and diodrast in doses comparable to that given infants of the same weight, i.e., 9.7 cc per kilogram. Cystograms and cystometrograms were made by introducing a No. 16 Foley catheter into the bladder in the female dog, or by means of a No. 5 ureteral catheter in the male dog. Residual urine and bladder capacity were estimated at this time. At sacrifice the entire genito-urinary tract and graft area with its mesenteric pedicle were removed and sectioned. To determine the absorptive pattern of the graft, blood chemistries including urea nitrogen, chlorides and carbon dioxide combining power were taken preoperatively and at intervals throughout the follow-up period. Sodium and potassium levels were similarly obtained.

RESULTS

Five dogs were sacrificed at 1 week, 3 weeks, 7 weeks, 3 months and 3½ months respectively. The five remaining dogs were alive and healthy after two and one-half to four months postoperatively. The results of the 10 dogs used in this series are presented in table 1. In 2 cases low grade urinary tract infection was noted which readily responded to chemotherapy. Postoperative intussusception developed in one instance and the animal was sacrificed at 1 week.

TABLE 1 *Summary of results*

Dog	Sex	Weight lbs	Result	Interval	Complications	Bladder Capacity cc	Post Op Days	Residual Urine
7	M	20	sacr	3½ mos	low grade urinary tract infection	125 130	10 115	none none
14	F	30	sacr	3 mos	none	80	41	none
11	F	28	1 & w	4½ mos	transient hydronephrosis	150 150	40 90	none none
8	M	25	sacr	3 wks	none	125	21	none
6	F	30	1 & w	3 mos	none	115	79	none
1	F	25	sacr	1 wk	intussusception of ileum			
5	M	29	1 & w	3 mos	none	80	71	none
10	M	23	sacr	7 wks	localized peritonitis	—		
11	M	27	1 & w	2½ mos	low grade urinary tract infection	60	63	none
13	M	19	1 & w	2½ mos	none	120	61	none

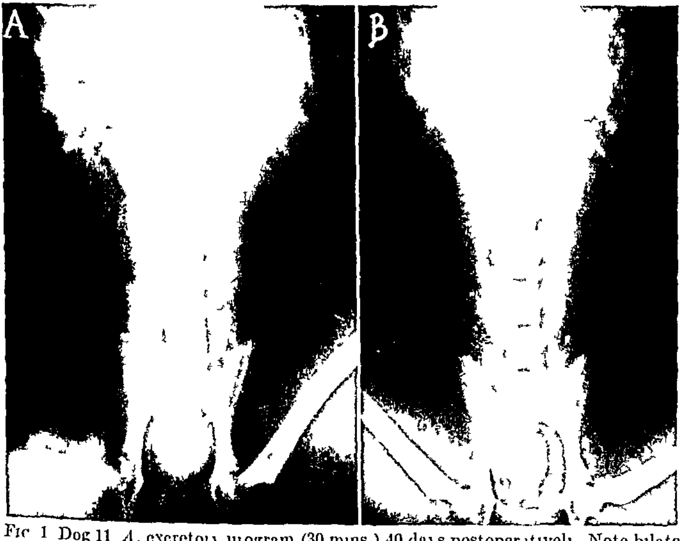

FIG 1 Dog 11 *A*, excretory urogram (30 mins) 40 days postoperatively Note bilateral upper tract dilatation *B* excretory urogram (30 mins) 116 days postoperatively Note normal upper tract

The anastomotic site was well healed and no obstruction or infection of the urinary tract was found One dog sacrificed at 7 weeks was found to have a low grade, localized peritonitis apparently arising at or near the intestinal flap See table 1

Suprapubic fistulas closed spontaneously within seven days after removal of the tube. Urinalyses taken at intervals postoperatively showed no gross or microscopic abnormalities except in the two animals in which a transient low grade urinary infection developed.

Objective study of the animals showed that there was no incontinence, frequency or retention. Immediately after voiding the dogs were catheterized, on several occasions, for residual urine. At no time was residual urine found.

Excretory urograms showed bilateral hydronephrosis and hydro-ureters (fig. 1, *A*) in only one dog 3 weeks postoperatively; subsequent study taken at the end of the 3 months showed return of the upper urinary tract to normal (fig 1, *B*). The cystograms showed smooth bladders (fig. 2) in 9 cases and a somewhat deformed bladder in one case. There was no functional disability in any of the dogs in the series. Cystometrograms (fig 3, *A*) showed apparently normally functioning bladders.

Results of the blood chemistry determinations reveal comparatively normal urea nitrogen levels and electrolyte balance in all dogs when follow-up values are compared with preoperative controls (fig. 3, *B*). Minor initial postoperative elevations of blood urea nitrogen were noted in 5 dogs. In six of 8 cases followed over two months the final urea nitrogen level was lower than the preoperative value, while in the remaining two dogs final values were only slightly higher than the controls. In one instance there was an elevation of the carbon dioxide combining power above the control level, in a dehydrated dog on the seventh postoperative day. This promptly fell to normal after adequate hydration. Chloride levels remained in the range of the preoperative controls. In no instance were we able to find hyperchloremic acidosis or uremia.

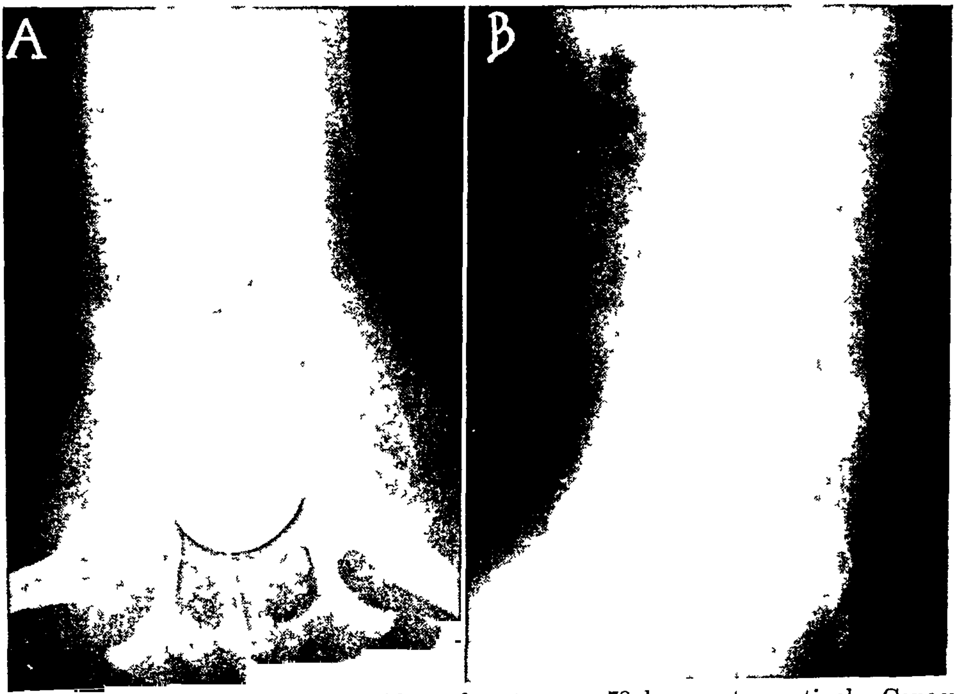

FIG 2 Dog 6 Anteroposterior and lateral cystograms 78 days postoperatively. Capacity 150 cc Note smooth bladder and lack of reflux

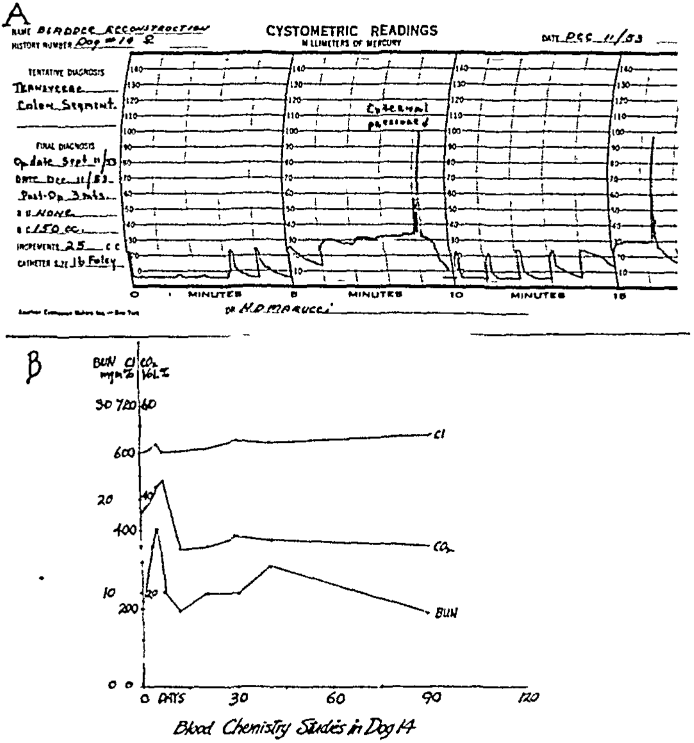

FIG. 3 Dog 14. *A*, cystometrogram 90 days postoperatively. *B*, graph of blood chemistry determinations.

Necropsy studies showed grossly normal genito-urinary tracts (fig. 4) with viable intact grafts in all cases. Sections of the kidney taken routinely appear normal. All of the bladders were well healed. The animals sacrificed at 1 and 3 weeks postoperatively showed a roughened area in the bladder mucosa probably due to catheter edema. There was no marked gross delineation between the graft site and remnant in these animals. The vascular pedicle appeared grossly normal. There were a few soft adhesions between the graft and loops of intestine on the abdominal aspect of the graft.

Histological sections made of the graft areas show gradual development of transitional cell epithelium in the area previously occupied by serosa (fig. 5). This change begins early and is apparently complete at seven weeks. Intact muscular layers and abundant vascularity were noted in all instances. The outer layer of the reconstructed bladder becomes covered with loose areolar tissue.

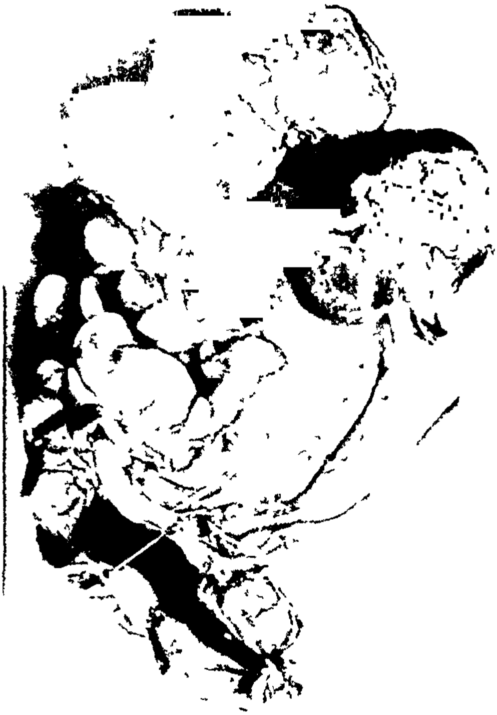

FIG. 4. Dog 7. Gross specimen of urinary tract. Animal sacrificed 3½ months postoperatively. Bladder capacity 150 cc.

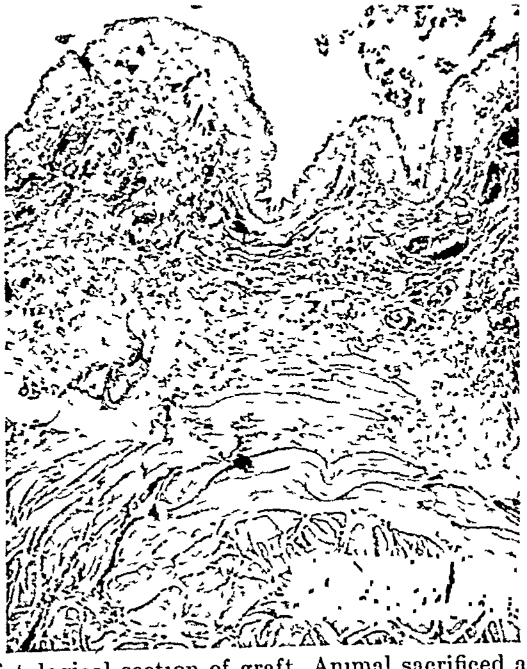

FIG. 5. Dog 14. Histological section of graft. Animal sacrificed at 3½ months. Transitional epithelium covers serosal surface of graft.

DISCUSSION

Repair of bladder defects has been met with considerable difficulty in the past Ascending infection, the production of mucus and absorption of electrolytes and nitrogenous wastes, may preclude satisfactory results We have been unable to find any reports in the literature describing the use of intestinal segments devoid of mucous membrane, or the serosal aspect of intestinal segments applied to the luminal surface in a reconstructed bladder A new method of repair of surgically created defects in the urinary bladder of dogs, using segments of intestine in which the mucous membrane was stripped from the seromuscular coat, has been described In this technique the serosal lining was placed on the luminal side of the newly reconstructed bladder Our experience in this preliminary experimental study leads us to believe that the seromuscular graft satisfies all of the previously posed criteria for an ideal tissue graft Subtotal resection of the bladder leaving only the trigone and a narrow margin around the urethra and ureteral orifices was used in this study, because it was felt that complete cystectomy might interpose the factors of obstruction and infection inherent in the problem of ureteral anastomosis However, we have already performed complete cystectomies and anastomosis of ureters into a substitute seromuscular bladder in a series of dogs The results of these experiments have not been completely satisfactory with regard to ureteral implantation This we feel is a problem of technique which is being remedied in a current study

CONCLUSION

Criteria of material for an ideal bladder graft have been listed and a new method for bladder reconstruction fulfilling these requirements has been described

A series of 10 dogs with bladders reconstructed using the seromuscular graft technique were observed during a four month follow up period Resultant normal voiding ability, absence of residual urine, blood chemistry studies, urograms, cystograms and cystometrograms indicated essentially normal dynamics and urinary tract function

Histological examination demonstrated overgrowth of the seromuscular graft by transitional epithelium, preservation of musculature and rich vascularity of the intact viable graft

Further application of this technique is being studied

The authors wish to express their gratitude and appreciation to Dr Edward W Campbell and Dr G John Gislason of the Department of Urology and to Drs William L Martin, Paul D Grotzinger and Alex W Uhn of the Department of General Surgery for their guidance, advice and encouragement

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URINARY AND FECAL INCONTINENCE DUE TO CONGENITAL ABNORMALITIES IN CHILDREN: MANAGEMENT BY TRANSPLANTATION OF URETERS TO AN ISOLATED ILEOSTOMY

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The combination of urinary and fecal incontinence due to congenital nerve defects presents a most difficult problem since the ureters obviously cannot be transplanted to the rectum or sigmoid by the usual manner.

When recently faced with two such cases, the most feasible solution to the problem seemed to us to be the use of the so-called Bricker procedure (fig. 1). In this operation a short segment of terminal ileum is isolated. The proximal end of the segment is closed and placed at the sacral promontory and the open distal end is led out through the abdominal wall. The ureters are transplanted to the proximal portion of the isolated ileum which then acts as a conduit from the ureters to the skin where the urine can be collected in a skin-adherent ileostomy bag. According to Bricker, this procedure was first carried out clinically by Dr. Heinz Haffner of St. Louis.

Without treatment, these patients are uncomfortable because of constant soilage and skin maceration. They are malodorous, socially unacceptable, and unable to indulge in many of the activities of a normal life. They are frequently severely ill because of urinary infection and the eventual outcome in many cases is death from renal failure.

We present our experience in support of the idea that the Bricker procedure might have wider application.

CASE REPORTS

Case 1. No. A-5636. A. P. was born with complete exstrophy of the bladder, unusually wide separation of the symphysis pubis, imperforate anus and rectoperineal fistula, bifid scrotum, bilateral inguinal hernias, spina bifida occulta with a hemivertebral deformity of the third and fourth lumbar vertebrae, and a left club foot.

At 2 months of age the hernias were repaired and then, at a separate procedure, an attempt was made to correct the imperforate anus and fistula. A functioning sphincter was not obtained, probably because of a nerve defect related to the spina bifida.

At 16 months, excretory urography (fig. 2, *A*) showed grade 3 ureterectasis and caliectasis with bilateral ureterovesical obstruction. The blood urea nitrogen was 40.0 mg. per cent. A bilateral uretero-ileostomy was then performed after the method of Bricker. The postoperative course was uncomplicated. One

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Read at annual meeting, Western Section of American Urological Association, Victoria, B. C. April 19–22, 1954.

We wish to acknowledge the kind assistance of Dr. Belding H. Scribner of the U. S. Veterans Administration Hospital, Seattle, for his assistance with some of the chemical determinations.

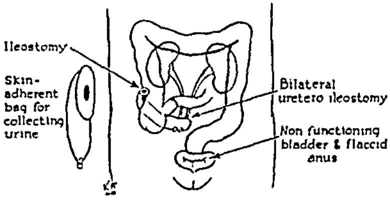

Ileostomy
Skin-adherent bag for collecting urine
Bilateral uretero ileostomy
Non functioning bladder & flaccid anus

FIG. 1

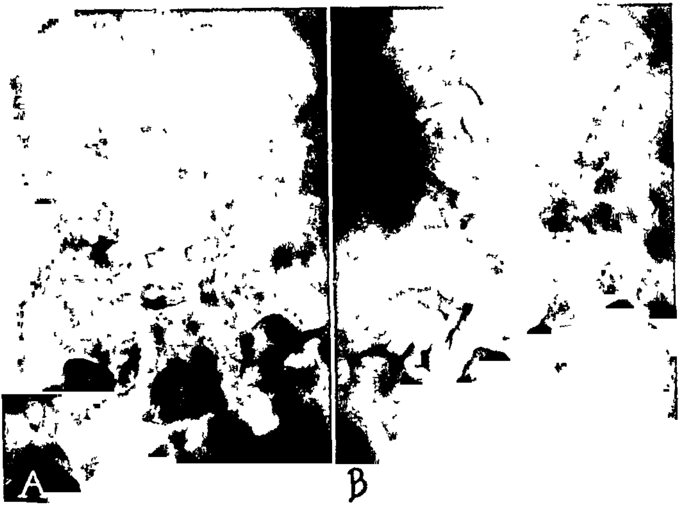


FIG. 2

month after surgery excretory urography showed a definite decrease in the dilatation of the right upper tract. Grade 3 dilatation, however, persisted on the left. The exstrophied bladder was removed when the child was 27 months old (10 months postoperative) and pyelograms at this time showed grade 1 dilatation bilaterally. At 30 months (13 months postoperative) the pyelograms (fig. 2, *B*) were interpreted as essentially normal. At 32 months (15 months postoperative) the plasma CO_2 combining power was 26.0 mEq./L (normal 25–30 mEq./L); blood urea nitrogen 17.0 mg. per cent; chloride 103 mEq./L (normal 98–106 mEq./L); sodium 142 mEq./L (normal 135–145 mEq./L); potassium 4.3 mEq./L (normal 3.5–5.5 mEq./L).

An ileogram (fig. 2, *B*) showed a segment of ileum which irregularly traversed the right lower quadrant of the abdomen. Repeated catheterization of this has shown a residual urine of 0–3 cc. This would indicate that this segment of ileum acts primarily as a conduit and not as a reservoir, thereby reducing the op-

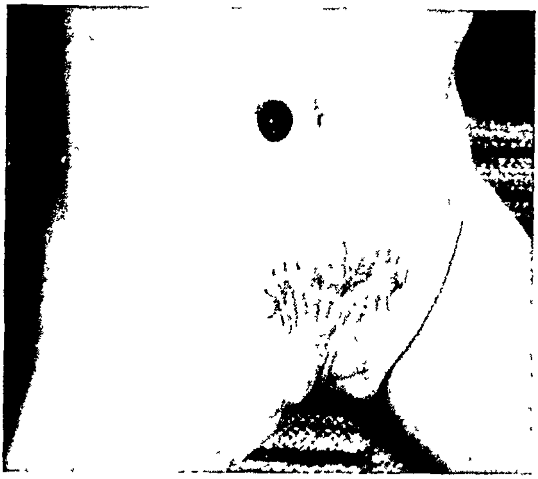


FIG. 3

portunity for re-absorption and also eliminating urinary stasis and resultant urinary infection.

The skin about the ileostomy has remained clean without ulceration or infection (fig. 3). The urinary discharge has been managed satisfactorily by the use of a diaper. When the child is older he will be fitted with an ileostomy bag. Fecal incontinence and impactions are now readily controlled by the use of a mildly constipating diet and simple daily enemas.

The improvement in his general condition has been striking. He runs and plays actively with other children and is healthy and happy. There has been improvement in his renal function and urinary tract infection has been absent.

Case 2. No. A-4340. I. A. was born with a myelomeningocele which was repaired at the age of 3 months. The child was paraplegic and had bilateral dislocated hips. She had had both urinary and fecal incontinence since birth. The rectal sphincter was flaccid and urine gushed from the urethra on light pressure over the lower abdomen. Chronic and recurrent urinary tract infection was controlled at first by gantrisin but finally became resistant to all urinary antiseptics.

At 3 years of age cystoscopy revealed severe cystitis. An excretory urogram (fig. 4, *A*) showed grade 3 dilatation of the upper urinary tract. The blood urea nitrogen was 11.6 mg. per cent. At the age of 3 years and 4 months the Bricker procedure was performed. The postoperative course was excellent.

Since surgery, the patient has had no further episodes of chills and fever. Chronic purulent cystitis of the unused bladder persisted for several months but appears to be controlled. Excretory urography 6 months postoperatively (fig. 4, *B*) shows essentially normal kidneys. At the time of writing (9 months following operation) her plasma CO_2 combining power is 23.0 mEq./L (normal 25–30 mEq./L); blood urea nitrogen, 12.0 mg. per cent; chloride, 102 mEq./L; sodium, 143 mEq./L; potassium, 4.7 mEq./L.

Clinically she has shown no signs of acidosis, and her general growth and development have been normal. Her bowels have been adequately controlled

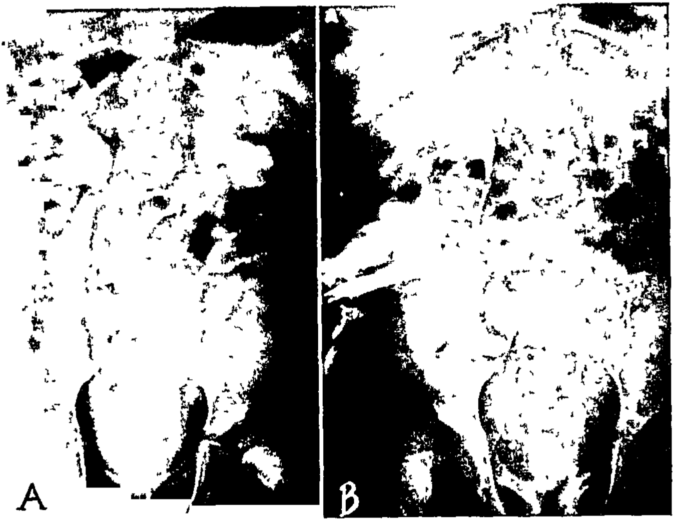


FIG. 4

by diet and daily enemas. There has been no skin maceration. Repeated residual urine determinations from the ileostomy have been less than 4 cc. Although E. coli were cultured from the ileostomy on one occasion she has shown no signs of upper urinary tract infection.

DISCUSSION

The chief problem in the management of these patients is to establish some kind of unobstructed urinary flow, and yet one which the patient can easily handle. The method selected should not leave the patient susceptible to urinary infection, electrolyte disturbance, or kidney damage. Where the fecal control is concerned we and others have found that most children with an incontinent anal sphincter can have good bowel control by the use of a constipating diet together with regular enemas.

The alternatives which could be considered for urinary diversion include (fig 6): 1) bilateral skin ureterostomies or nephrostomies, 2) a permanent suprapubic cystostomy, 3) "muscle sling", and other urinary sphincter reconstruction procedures, 4) ureterosigmoidostomies with a left lower quadrant end sigmoidostomy (so-called "wet colostomy"), 5) transplantation of the ureters into an isolated pouch of large bowel (i.e. isolated sigmoid pouch or cecal pouch), and finally 6) the use of a segment of ileum as a conduit from the ureters to a collecting bag on the skin (the Bricker procedure).

The procedure which we have used in our 2 cases was described by Bricker in connection with patients requiring removal of the bladder and rectum for

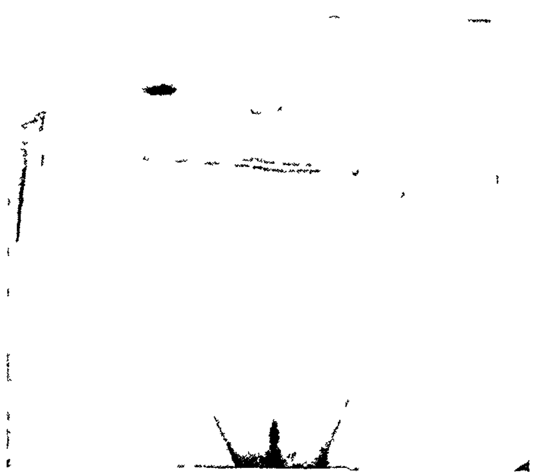
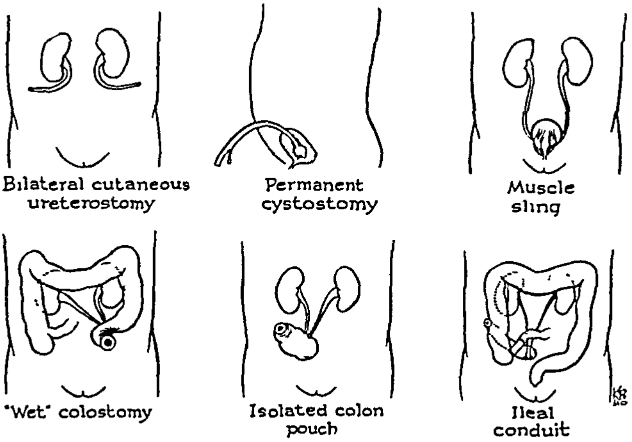


Fig. 5



Bilateral cutaneous ureterostomy

Permanent cystostomy

Muscle sling

"Wet" colostomy

Isolated colon pouch

Ileal conduit

Fig 6

carcinoma. This method employs an isolated piece of ileum to lead the urine from the ureters out to a position on the anterior abdomen where a plastic, easily removable collecting bag can be cemented to the skin. The piece of ileum is not intended to act as a reservoir or artificial bladder but rather as a tube from the ureters to the abdominal wall.

A theoretical objection to this procedure lies in the possibility of excessive absorption of urinary constituents by the segment of ileum. In this regard Reiger et al. have shown in experiments on dogs that an elevated blood urea nitrogen and depressed CO_2 combining power are definitely related to the length of small bowel exposed to the urinary stream. Ileal loops greater than 35 cm. in length were not compatible with life. Merscheimer et al., using a 10 cm. length of ileum for bilateral ureteral transplants in dogs, report no evidence of infection and normal pyelography and blood urea nitrogen determinations after an 18 month period of observation. Our ileal segments were 35 cm. and 22.5 cm. long respectively. We have not found these to be too long as evidenced by the normal chemistries.

It is well known that urea and chloride are absorbed from isolated pouches of intestine when present in concentrations usually found in normal urine.

Three different factors contribute to electrolyte re-absorption 1) the concentration of the electrolyte in the urine, 2) the length of time the urine remains in contact with the absorbing surface of the intestinal tract, 3) the area of intestinal mucosa exposed to the urine With hydration, electrolyte re-absorption will be kept at a minimum Since prolonged pooling of urine leads to electrolyte re-absorption, frequent emptying of urinary pouches is advised and by employing a short piece of intestine it acts as a conduit rather than reservoir This in turn furnishes a relatively small absorbing surface and minimizes electrolyte absorption

That stasis has not been present in our cases was demonstrated by the finding of only 1 cc of residual urine or less on repeated catheterization of the ileostomies Lack of stasis, a short length of bowel and isolation from the fecal stream, have all contributed to the successful outcome in these children

Our 2 cases have shown gratifying clinical results Each child has shown marked clinical improvement following the operation In both cases there was severe bilateral hydronephrosis which subsided following surgery In Bricker's experience, 86 per cent of all ureters, including the hydronephrotic ones, are either normal or show minimal hydronephrosis 6 months to 1 years following transplantation

The incidence of infection is low Recognizable pyelonephritis occurred in only 12 cases out of 65, in a long term follow-up study In 51 cases reported by Bricker, there has been no case of hyperchloremic acidosis

Our 2 patients have been free from urinary infection since surgery whereas before surgery urinary infection was ever present Blood urea nitrogen determinations have become normal following surgery in one patient and have remained normal in the other From the point of view of convenience to the patient and the parents, these two children have required little extra care Their diapers are at present worn on the abdomen and skin maceration has not occurred in either case The manufacturer of the plastic bags is tentatively planning to fit these children with their appliances at 5 years of age

Cordonnier has utilized the ileal segment for carcinoma of the urinary bladder in 19 cases Although it is too early to evaluate his results as far as cancer surgery is concerned, he believes that the results are highly satisfactory He maintains that the principal advantages of the Bricker operation are the complete elimination of the electrolyte imbalance and reduction in the amount of urinary sepsis

SUMMARY

The case histories of two children with both urinary and fecal incontinence due to congenital abnormalities are presented The ureters were transplanted into one end of an isolated segment of ileum which was then brought out on the abdominal wall to act as a urinary conduit (the Bricker procedure) The fecal incontinence has been readily handled by a mildly constipating diet and simple enemas

Previously existing hydronephrosis has improved in each case

Previously present urinary infection has been eliminated

The blood electrolyte patterns have been found to be normal 9 and 15 months after operation.

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SURGICAL TREATMENT OF HYPOSPADIAS

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It has only been during the past 10 years that men experienced in the surgical correction of hypospadias have published critical reviews of their methods of treatment based on series of twenty to fifty or more cases. We can now evaluate more clearly that which is good and that which is unsatisfactory.

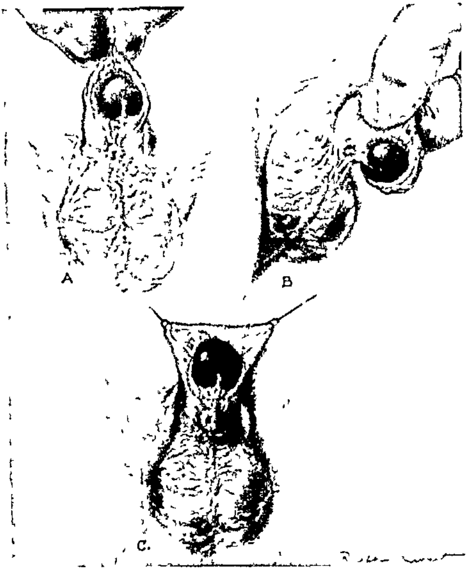

FIG 1. First stage. Typical deformity of hypospadiac penis showing ventral chordee, abnormally placed meatus, and hooded dorsal foreskin. Dotted lines indicate incision. (From Smith and Blackfield, Surgery, 1952.)

In the recent past I have had occasion to criticize the Browne modification of the Duplay-Marion operation. Since then Johanson has published careful follow-up studies on the 50 cases originally reported by Browne. He concluded that the results were excellent. Fogh-Andersen has also described very good results with this method. Of 34 patients so treated, fistulas developed in only 12 per cent. The caliber of one urethra, portrayed by urethrography, was of normal size. Gelbke has reported considerable success with this procedure, as have a good many surgeons in this country. The incidence of fistulas appears to be in the neighborhood of 15 per cent.

Read at annual meeting, American Urological Association, New York, N Y June 3, 1954.

The other type of repair which has proved satisfactory makes use of a completely formed urethra comprising penile skin which is covered by a scrotal flap. Using scrotal integument allows the formation of a urethra of wide caliber. (Blair, Cecil, Culp, Goodhope, Wehrbein, Smith.) Byars, however, has been able

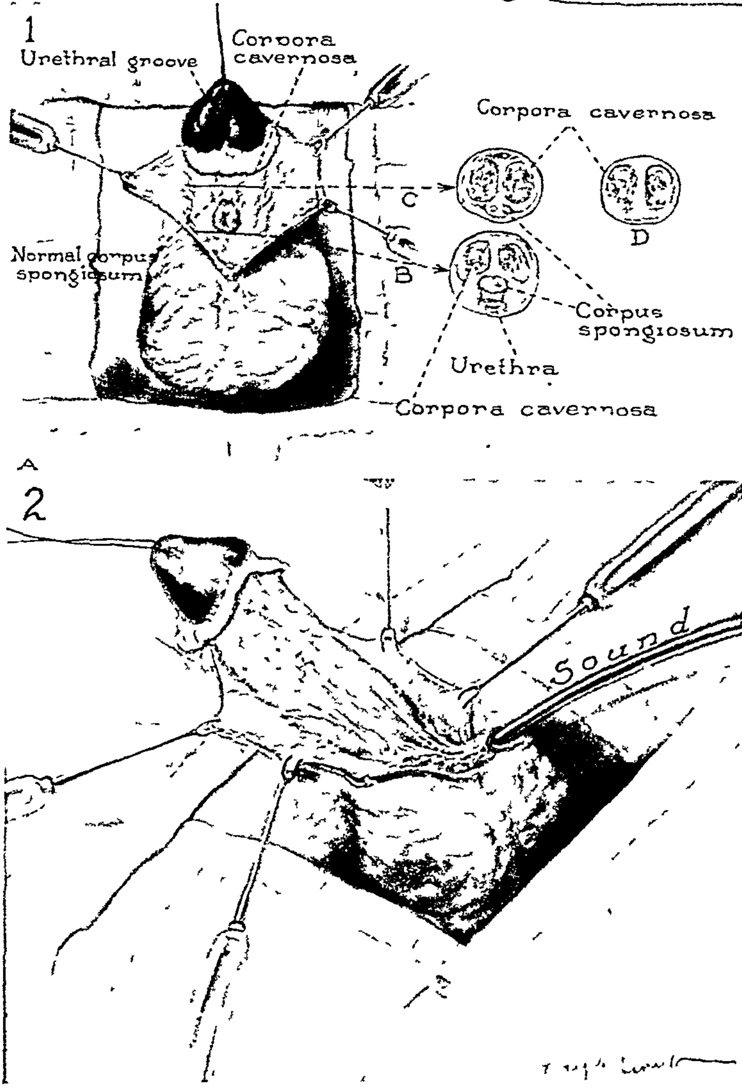

FIG. 2. *1*, Anatomy of hypospadiac penis *A*, shaft laid bare, chordee reduced. Normal corpus spongiosum occupying midline. *B*, cross section of proximal shaft showing corpora cavernosa and corpus spongiosum with urethra external to it. Urethra is attached to spongiosum by two fibrous bands. Fibrous connective tissue occupies crevasses where corpora meet. *C*, cross section distal to hypospadiac orifice. Corpus spongiosum is present. It is not fibrosed. *D*, at times, spongiosum is absent. Light band of connective tissues lies between two corpora cavernosa

2, Circumferential incision made just proximal to corona Foreskin is dissected from shaft Incision carried proximally on ventrum and extended just beyond it. Considerable cuff of skin should be left about meatus so that suture lines do not encroach too closely upon it; stricture might result. Skin flaps are freed by dissection with small scissors. Skin edges handled with double hooks. Fibrous bands between corpora should be sought and resected It may be necessary to free distal urethra and shift it posteriorly to complete correction of chordee. (From Smith and Blackfield, J. Urol 1948.)

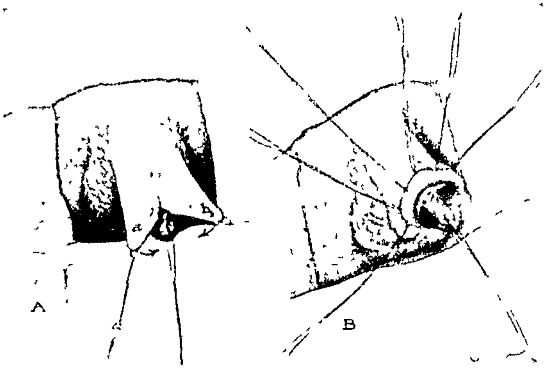

FIG. 3. *A*, area of ventrum thus increased requires more skin for cover. This is obtained by separating double fold of foreskin thereby converting it into single layer. This redundant flap is split down midline 2 to 3 cm. so that *a* and *b* meet at frenum without constricting shaft yet affording an adequate and loose cover for ventrum. If more is needed here, dorsal slit is further deepened. Tips of *a* and *b* should be excised; their blood supply often is impaired. *B*, adjacent skin edges at corona and on ventrum are sutured with nonabsorbable material. (From Smith and Blackfield, J. Urol. 1948.)

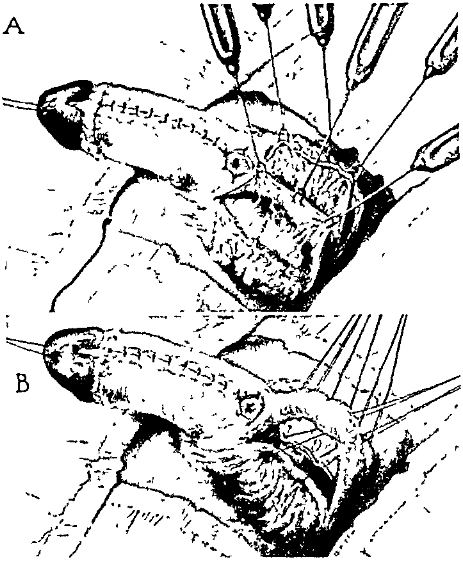

FIG. 4. *A*, Wehrbein scrotal tube pedicle Width of flap is equal to at least one-half circumference of penis and should be marked out without any traction being placed on scrotum Tube of too small diameter is worthless

B, this strip of skin is freed from scrotum and formed into tube with skin on its external surface Catheter should be placed at this time so that urethra will not be accidentally injured. If orifice should lie on penile shaft, tube shou[illegible] junction. Incisions are covered with zeroform gauze and [illegible] with biased stockinet. Penis is in dorsal position Dressin[illegible]ed in 8 days. (From Smith and Blackfield, Surgery 1952.)

to cover the new urethra successfully with the lateral penile skin flaps. The incidence of fistulas with these procedures is also about 15 per cent.

I have had occasion to repair the hypospadiac penis of 62 boys. The urethral tube has been completely formed from the ventral skin and the resultant defect has been covered with scrotal integument. Eighteen of these patients were treated by the three-stage procedure described by Blair. In the remainder (44) a modified two-stage Wehrbein operation was used.

TREATMENT OF CHORDEE

It has not been uncommon in the history of medicine for misinformation to be repeated from paper to paper and from textbook to textbook. This is certainly true so far as descriptions of the cause for the chordee are concerned. It is claimed that the penis is foreshortened ventrally because the rudimentary corpus spongiosum has undergone fibrosis and, therefore, contracture. Medical illustrators have been compelled to draw a heavy band of fibrous tissue lying in the midline distal to the meatus. I have corrected the chordee of 73 young boys; I have found this heavy band of tissue in only 3. They had scrotal hypospadias.

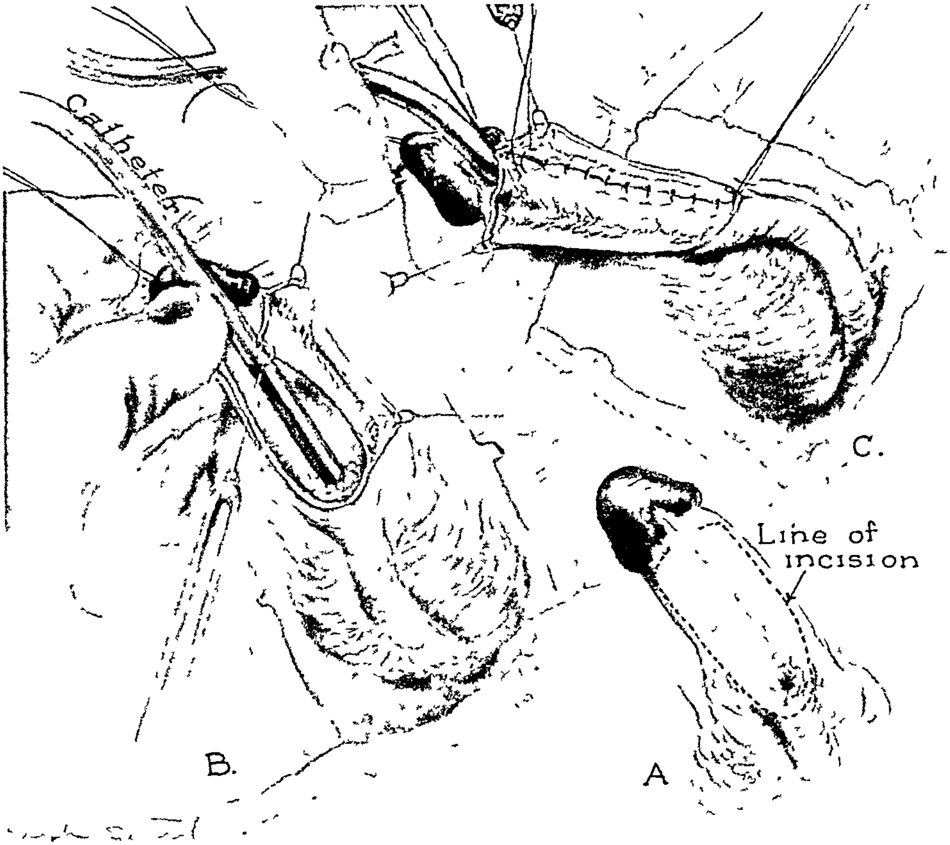

Fig. 5. Second stage (Duplay-Wehrbein) *A*, U-shaped incision Width of this flap should equal two-fifths to one-half circumference of penis thus furnishing urethra of wide caliber Small catheter is placed in bladder *B*, *C*, urethra formed with Lembert sutures of No. 0000 ureteral gut on atraumatic needles. Care is taken to invert edges of skin Urethra in region of abnormal meatus should be further re-inforced with second suture layer for fistula sometimes develops here. (From Smith and Blackfield, Surgery 1952)

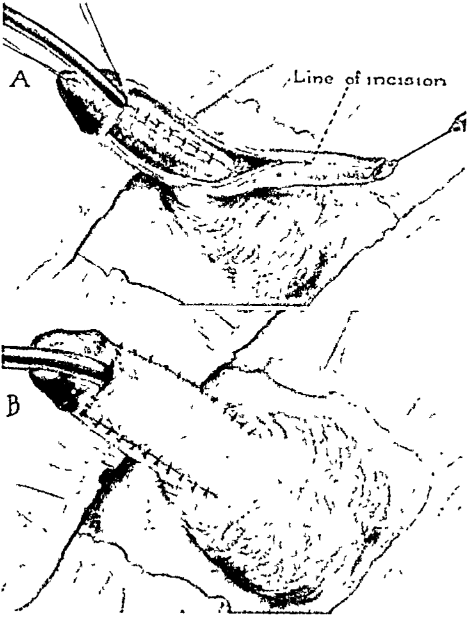

FIG. 6. *A*, distal end of tube divided. Cleavage plane is formed down its core from penile end and tube is opened. If meatus is on shaft, proximal penile skin is incised in midline and this incision is extended into tube. (From Smith and Blackfield, Surgery 1952.)
B, [illegible] nile [illegible] is a [illegible] (From Smith and Blackfield, Surgery 1952.)

Normally the skin of the penis slides easily on the shaft. This is not true of the skin distal to the abnormally placed orifice; it is tightly adherent to the underlying fascia. Separation of this skin from the shaft will reduce the chordee almost completely in most instances. Furthermore, close inspection will reveal that a normal corpus spongiosum is almost always present in the midline (fig. 2, A). It is not fibrosed. It is quite apparent that the urethra has left the corpus and become subcutaneous. The urethra is attached to the corpus by two fibrous bands (fig. 2, B). Between the three corpora (ventro-laterally) a normal amount of connective tissue is present. Division and resection of these small bands may further elongate the ventrum (fig. 2, C).

At times, the corpus spongiosum is absent. In this case, fibrous connective tissue occupies the crevass between the corpora cavernosa (fig. 2, D). The chordee may be further reduced by excising this tissue which is about 1 mm. thick.

The size of the ventrum increases as the chordee is reduced; this defect requires mobilization of skin from some other area. The redundant prepuce is an ideal source since it is thin, resilient and hairless. It will later be incorporated in the urethroplasty as a complete tube. The procedures described by Blair and by Nesbit are therefore admirably suited to the repair of the chordee.

On occasion, the distal urethra is roofed over by attenuated mucosa and skin which must be split open back to tissue of normal thickness. At times, meatotomy will be required since stenosis is not uncommon.

I am convinced that the repairs should be complete by the time the child reaches school age; the chordee is corrected at the age of 18 months. If the penis is smaller than normal (and it is apt to be in the more severe grades of hypospadias) growth can be stimulated by the daily administration of 5 mg. of methyl testosterone by mouth. This should cause a few erections daily. If erections are almost constant, the dose should be reduced. Androgen therapy may be necessary for as long as 6 months.

The chordee is repaired by the Blair procedure (figs. 1, 2, 2 and 3). In addition, a tube pedicle on the scrotum is developed after the method of Wehrbein (fig. 4).

The final stage is performed when the boy is 4 years old. A Duplay urethroplasty is utilized and the ventral defect is covered by the scrotal flap (figs. 5 and 6).

The repair of the hypospadiac penis in 44 boys has been completed by this method. In 5 cases one fistula developed; another had two. These were successfully closed. None have required sounds, for the urethral caliber is at least 20F. Some of these patients are now married and have children. This is the test of the functional result.

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CONSTRUCTION OF URETHRA IN HYPOSPADIAS USING VESICAL MUCOSAL GRAFTS

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The presentation of another technique for the construction of a new urethra in cases of hypospadias seems justified by the reasonably satisfactory results that have been obtained in twenty-six cases. The mucosa of the urinary bladder appeared to be particularly suitable material. Certainly this mucosa is plentiful, easy to obtain and, in most cases, sterile. Surely it would not produce hair, and excoriation and desquamation from exposure to the urine would not be expected. Furthermore, bladder mucosa, being soft, pliable and elastic, might remain so after transplantation.

In recent times we have favored the correction of the chordee after the method described by Nesbit[1] (fig. 1). This method limits the cutaneous scar tissue on the ventral surface to a small transverse area and provides excellent correction of the curvature. In December 1947 a segment of vesical mucosa was transplanted as a free tube graft about a splinting catheter through a *subcutaneous* tunnel in the ventral surface of the penis (J. S. NYH No. 482181). The proximal end of the graft was anastomosed to the partially amputated hypospadiac urethra in an end-to-end manner. Urinary diversion was supplied by cystostomy. The splinting catheter was removed on the seventeenth postoperative day and the suprapubic tube the following day. The cystostomy opening closed at once and the patient voided without difficulty from the glandular meatus, without the presence of fistula or stricture.

Memmelaar[2] also found that the bladder mucosa transplanted readily as a tube into a longitudinal incision on the ventral surface of the penis. The possibility of fistulas along the body of the graft would seem to be lessened by leaving the skin and subcutaneous tissues intact over this distance rather than performing the long, trough-like incision of Memmelaar. In fact, in our twenty-six consecutive cases in which the graft has been placed through a subcutaneous tunnel, not one fistula has developed along the body of the graft (exclusive of the ends of the graft).

The possibility of bone formation was brought to our attention by the work of Huggins[3, 4] and Copher.[5, 6, 7] These workers demonstrated that a flat piece of

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Read at annual meeting, American Urological Association, New York, N. Y. June 3, 1954

[1] Nesbit, R. M.: Plastic procedure for correction of hypospadias. J. Urol., 45: 699–702, 1941

[2] Memmelaar, J.: Use of bladder mucosa in a one stage repair of hypospadias. J. Urol., 58: 68–73, 1947

[3] Huggins, C. B.: The formation of bone under the influence of epithelium of the urinary tract. Arch. Surg., 22: 377–408, 1931

[4] Huggins, C. B.: Bone and calculi in the collecting tubules of the kidney. Arch. Surg., 27: 203–215, 1933

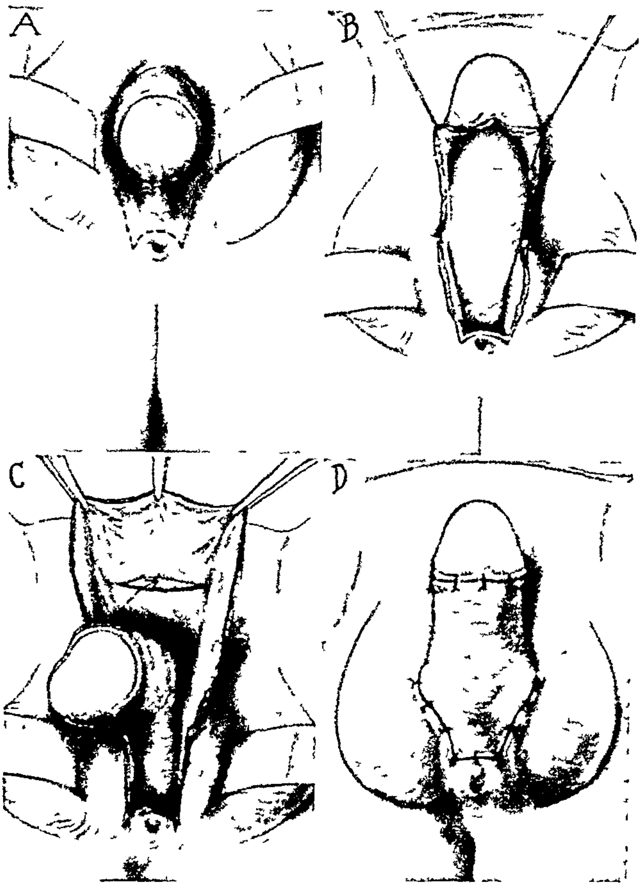

FIG. 1. Correction of chordee. *A*, *B*, *C*, method of developing and perforating dorsal skin flap following excision of ventral fibrous tissue. *D*, approximating skin edges Note that linear ventral scar in skin is avoided. After Nesbit.

vesical mucosa of a dog buried in connective tissue of certain locations routinely resulted in the transition of such connective tissue into actual bone. Forty-seven transplantations of free bladder mucosa were carried out by us in dogs. Forty-three of the grafts were transplanted successfully, i.e., they were "takes." Bone formation was induced only when the connective tissue was directly exposed to the mucosal surface. Actually the grafts, both here and in the human cases, consist not only of the transitional epithelium but also of some submucosa. If a tubular graft was transplanted with the transitional celled surface facing the lumen, and opening to the exterior, no bone formed in any case. Also, if a continuous cyst with the transitional celled surface inside was transplanted into a usual site for bone formation (just over the rectus sheath) no bone was found in any case. Contrariwise, if the transitional celled surface was placed on the out-

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[5] Copher, G H and Key, J. A : Influence of bladder transplants on the healing of defects of bone Arch Surg , **29:** 64–76, 1934.

[6] Copher, G H.: The influence of urinary bladder transplants on hyaline cartilage. Ann. Surg , **102:** 927–939, 1935.

[7] Copher, G. H · The effect of urinary bladder transplants and extracts on the formation of bone (an experimental study). Ann. Surg. **108:** 934–940, 1938.

side of either the tube or cyst, i.e., in direct contact with the adjacent connective tissue, bone formation resulted routinely. Thus it seemed impossible that bone would form in the human so long as the mucosal surface faced the lumen and no bits of epithelium became buried against connective tissue without drainage to the exterior.[8] In twenty-six consecutive human cases in which we have used vesical mucosal grafts for the construction of a new urethra, there has been no clinical evidence of bone formation.

Encouraged by the results in the first case and supported by the findings in the animal experiments, twelve additional patients were operated on using this early technique. The patients ranged from six to thirty-seven years of age. The meatus was midshaft in two, penoscrotal in seven, and perineal in four. Three patients had had previous attempts to construct a urethra from skin. Although all grafts in this original series survived in their entirety and although no fistulas or strictures occurred along the body of the graft, the occurrence of complications at each end of the graft was not unusual. At the distal meatus four strictures occurred, but all were readily corrected by meatotomy. At the proximal end of the graft, i.e., at the juncture of the graft and the urethra, six fistulas occurred. One of these fistulas healed spontaneously within two weeks and the patient has had no other complications over the next three years (P. S. NYH No. 323810). An almost microscopic fistula at the junctional area has remained unchanged over a 7-year period because the patient (C. S. NYH No. 428078) refused further treatment, having married and become a father during that time. On three patients, six surgical procedures successfully closed the fistula and these patients have now been followed for 3 years (H. W. No. 606254, R. W. No. 441552, R. W. No. 415856). The remaining patient with a fistula (R. O. No. 430380) had the only large one at the junctional area and this resisted two premature attempts at surgical closure. Subsequently closure was accomplished by Mr. Denis Browne[9] using his technique. Four strictures occurred at the junctional area. One of these (M. M. No. 597670) has been relieved for 3 years by one dilation under anesthesia. Another (W. M. No. 547377) has been relieved for 4 years following three dilations. A third patient with junctional stricture (W. B. No. 462847) has required no further therapy after two internal urethrotomies, the follow-up period now being 3 years since the last procedure. The fourth stricture occurred in a complicated case (R. H. No. 371016) in which six previous attempts to construct a urethra from the perineal meatus, using skin, had failed. Several remnants of skin tubes were excised at the mucosal grafting operation, but a stricture and the only diverticulum in this series developed at the junctional area. These were surgically corrected but urethral dilations have been required approximately every six to eight weeks over the succeeding four years, this being the only patient now receiving dilations. Another patient (C. K. No. 498513) had a peculiar, but fortunately transient, valve like obstruction at the junctional area which was relieved following two apparently unrevealing endoscopic examinations. Four years later the patient has an occasional dribble but has a good stream, clear urine, and no evidence of stricture or fistula. Severe bladder spasms occurred in one patient (A. K. No. 389920) with an hysterical type of personality, so that it was necessary to make a perineal urethrostomy which is his present functioning meatus, although a mucosal-lined urethra is present from the urethrostomy to the glans. Thus, nine of the original thirteen patients now have achieved a satisfactory result. By satisfactory result is meant that the penis is straight, there are no fistulas or strictures, the meatus is at or on the glans, the urethra is without hair, the stream is good, and the urine is clear. To this group may be added the case of R. O. whose fistula was subsequently closed by the Denis Browne procedure. Three unsatisfactory results are in the patient who will not permit closure of his minute fistula, the patient requiring dilations, and the patient currently with the urethrostomy. The follow-up period varies from three years to over seven years in these cases.

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[8] Marshall, V. F. and Spellman, R. M. The use of bladder mucosa for the construction of a urethra in hypospadias. Scientific exhibit, Am. Urol. Ass'n., Atlantic City, 1952.

[9] Browne, D. Personal communication, 1954.

Although most of the complications were fairly readily and apparently permanently overcome, it became apparent that an improved method for managing the ends of the grafts was highly desirable, since all of the difficulties had occurred either at the junctional area or at the new meatus. In the early technique the original urethra and the graft were anastomosed end-to-end and this anastomosis was situated in a potentially large dead space. Perhaps also, the graft at the anastomotic site was not sufficiently supported by immediately adjacent tissues. Furthermore, the suture line of the skin was immediately over the anastomosis, thus encouraging fistula formation. At the distal or glandular end of the graft even a slight slough at the skin edge would leave a contracting ring of fibrous tissue which might result in stricture. Bearing these considerations in mind, the following technique was devised and has now been applied in another thirteen consecutive cases.

After the elapse of approximately six months from the time of chordee correction the second stage of the program is undertaken (figs. 2 and 3). The anesthetized patient is placed in a semi-lithotomy position with the buttocks elevated and slightly protruding over the end of the table. The field is prepared from

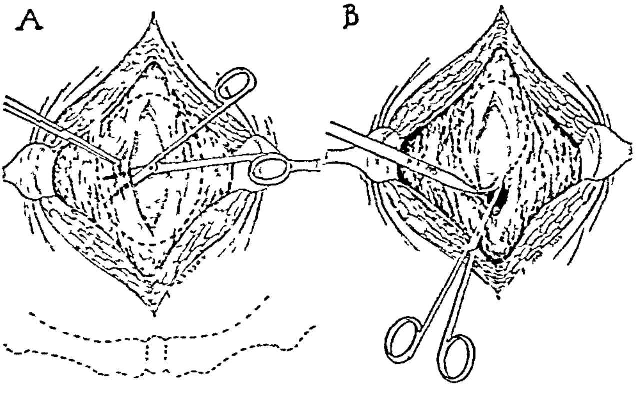

FIG. 2. Improved technique. *A*, suprapubic dissection of vesical mucosa from distended bladder wall. *B*, excision of mucosal and submucosal segment.

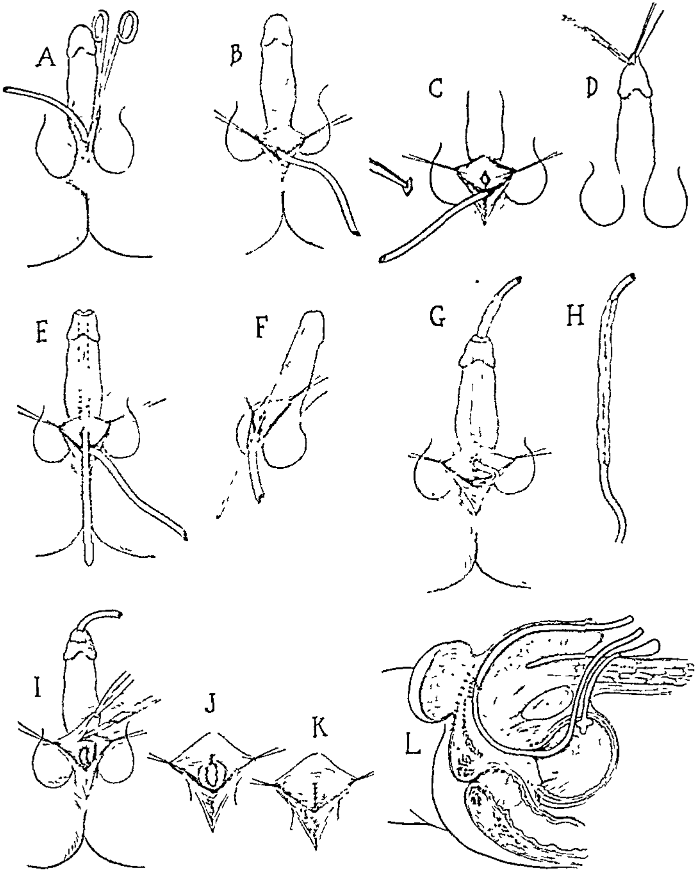

FIG. 3. *A* and *B*, opening of perineum and urethral floor. *C* and *D*, excision of mucosal patch in urethral roof and removal of small patch of skin from glans. *E* and *F*, development of submucous tunnel (between corpora cavernosa and skin). *G* and *H*, graft in place with proximal edge sutured to mucosal opening previously made, D, as splinting catheter is passed into bladder. *I*, *J*, *K*, excising excess mucosa except that necessary for a side-to-side closure. Eversion and suturing of graft on glans. *L*, cross section showing splint, graft, perineal closure and cystostomy tube.

above the umbilicus to well below the hypospadiac meatus. A catheter is inserted into the bladder which is distended with saline. The anterior bladder wall is exposed through the usual suprapubic incision. By sharp and blunt dissection a line of cleavage between the mucosa (with submucosa) and the muscularis is developed. This is usually easier than excising an oblong, full thickness segment of the bladder wall, pinning it to a board and dissecting the mucosa and submucosa off the muscle layer. This mucosal and submucosal graft tissue has surprising strength and is quite elastic. We have always obtained more than needed by excising the estimated length required and a width of about two centimeters from the distended bladder. A cystostomy catheter is placed, the inner end of the transurethral catheter (used to distend the bladder) brought out beside it, and the wound closed in routine fashion. The graft is stabilized by pinning it with fine needles to a moistened board. A latex catheter, usually 12F for children but larger for adults, is placed over the mucosal side of the rectangular strip of tissue to be grafted. The graft is made into a tube over the catheter by loose approximation with a continuous 6-0 atraumatic chromic catgut suture. Extraneous tissue adherent to the graft and irregularities are carefully trimmed away. At all times the graft is kept moist with warm saline.

A ventral midline incision of three or more centimeters is then made from the hypospadiac meatus backward through the skin, connective tissue of the perineum, and urethral floor. The inlying catheter is retracted toward the rectum, thus providing exposure of the mucosal roof of the natural urethra in its distal three or more centimeters. A circular or diamond-shaped piece of mucosa in the roof of the urethra at least one centimeter proximal to the mucocutaneous junction is then excised. The diameter of this bit of mucosa removed is intended to be slightly larger than the diameter of the splinting catheter to be used.

The skin is superficially removed for a radius of five or six millimeters about the urethral dimple on the glans. A sharp-pointed blade (No. 11, Bard-Parker) on a narrow handle is introduced at the most proximal edge of the prepared opening in the roof of the urethra. The knife is carefully passed subcutaneously along the ventral surface of the penis and out through the center of the prepared area in the glans, taking care not to buttonhole the skin or pass into the corpora cavernosa. The handle of the knife is grasped with a small clamp and the latter is guided through the tunnel. The tip of the splinting catheter and the graft are grasped with this clamp and drawn through the tunnel. Any damaged bits of the end of the graft are carefully excised. The graft is grasped on its most distal or glandular end with a small clamp and the well moistened splinting catheter is pulled through this mucosal sleeve toward the bladder for fifteen or twenty centimeters. The proximal end of the splinting catheter is now held upward for exposure, so one half of the circumference of the proximal end of the graft can be approximated to the mucosal edge of the proximal aspect of the diamond-shaped defect with 6-0 catgut sutures. The tip of the splinting catheter is next attached to the perineal end of the transurethral catheter and is introduced into the bladder and out the cystostomy opening by simple traction. The remaining circumference of the juncture of the graft and the urethra is then approximated. The incision in the natural urethra now appears similar to the usual external urethrostomy. The excess mucosa of this area is excised and the ventral urethral mucosa is closed over the splinting catheter with a continuous 6-0 atraumatic chromic catgut suture. The remainder of the perineal defect is closed in layers with interrupted 4-0 atraumatic chromic sutures. Both ends of the splinting catheter are joined over the anterior abdominal wall and secured to the cystostomy tube After excising excess graft at the distal glandular end, the tissue is fanned out over the prepared raw area and attached there with interrupted single sutures of 4-0 plain catgut A saline soaked gauze is placed over the glans and kept moist for the next four to five days No other dressings are applied except about the cystostomy wound.

Penile edema which may be quite marked usually subsides by the fifth day A mild degree of ecchymosis is common but actual hematoma formation has been rare, due no doubt to avoiding the corpora when making the subcutaneous tunnel The cystostomy tube is kept open at all times and is only irrigated on indication The patient is kept in bed for the first three or four days and then mobilized Prophylactic antibiotics are administered According to the appearance of the operative area, the splinting catheter is removed between the seventh and tenth days After twenty-four to forty-eight hours the cystostomy tube is clamped and the patient is allowed to void As a rule there is dysuria and often it is necessary to reopen the cystostomy tube for another 24 hours If all is then satisfactory the cystostomy tube is removed

Many of the complications in this series, and in the earlier series, can be attributed directly to anxious early instrumentation Occasionally the anterior meatus may require a very gentle dilation, but otherwise it is best to forego all instrumentation for at least two weeks, even to the extent of replacing the cystostomy tube if needed After the patient is voiding well he is discharged to be followed Excretory urograms have been routinely employed as a follow-up procedure and often an atraumatic voiding urethrogram can be obtained after the pyelogram when concentrated intravenous media (70 per cent urokon) are used

This improved technique has now been applied to thirteen consecutive patients ranging in age from four to thirty-one years The meatus was midshaft in one, penoscrotal in five, and perineal in seven There was one complete failure which yielded to a repetition of the technique J P (NYH No 70035), a 31-year old white man with a perineal hypospadias, had had at least twelve unsuccessful attempts to form a urethra from skin On the third postoperative day the splinting catheter was inadvertently disturbed and presumably the graft was damaged Eventually there was no demonstrable mucosa persisting Two months later the procedure was repeated and the patient, for the first time, voids from a glandular meatus without a fistula However, there is a stricture at the meatus and in spite of two meatotomies the patient dilates his urethra with a bougie as necessary to maintain a good stream In addition to this meatal stricture there were three others, all yielding satisfactorily to one meatotomy each (A K No 465673, A C. No 643942, and J P No 673738) At the junctional area four fistulas occurred but three of these healed spontaneously within two weeks and the patients have had no further complications over the ensuing nine or more months (R Z No 576878, M G No 574605, and D M No 644153) In the other case of fistula (D V No 320001), the opening was successfully closed at the first attempt and the patient has a satisfactory result one year later Four months after operation a small sterile abscess appeared in the perineum of one patient (J. H. No. 523811) which was incised and the patient has had no further complications over the succeeding year. The two poorest results were obtained on J. P. (No. 70035), whose case was just described, and in the case of a 7-year-old boy with a perineal hypospadias (F. W. No. 410788). This patient had a marked tendency to keloid formation and considerable peri-urethral thickening developed in the immediate postoperative period. The graft was instrumented during this time and there is now a 2 mm. area in the midshaft which is devoid of urethra, voiding being accomplished through a perineal urethrostomy. Surgical correction is anticipated. Four patients had no complications of any kind at any time during the immediate postoperative course and 6 patients have required no procedures of any type after the grafting operation. The patients in this series have been followed from four months to one year. We consider the results to be satisfactory at this time in 11 cases (the poor results being those in the cases of F. W. No. 410788, and J. P. No. 70035). By satisfactory is meant that the penis is straight, that there are no fistulas or strictures, the meatus is in the glans (not just short of it), the urethra is hairless, the stream is good, and the urine is clear. This latest technique appears as a definite improvement over the earlier one, most particularly at the anastomotic area. Several children in both series have passed through puberty following the procedure and, as might be expected from observing skin grafts, the new urethra has increased in size along with the rest of the organ. Particularly impressive has been the elasticity and distensibility of the new, hairless urethra. The absence of marked scarring and/or redundant longitudinal skin masses on the ventrum have been other attractive features.

This technique requires time and attention to detail. It has been a distinct improvement over our previous experience with several other techniques. However, this past experience does not include the simpler appearing and currently popular procedure of Denis Browne.[10] Further improvements are, of course, desirable.

SUMMARY

Free grafts of bladder mucosa have been used with reasonable success for the construction of a new urethra in cases of hypospadias. The program is planned as a two-stage procedure: correction of chordee, and construction of urethra. With one exception in 27 operations on humans the grafts survived. Nearly all complications have occurred at either end of the graft. The procedure is not surgically difficult and may be applied prior to school age. Although not ideal, the technique has represented an improvement in our experience.

[10] Browne, D.: An operation for hypospadias. Proc. Roy. Soc. Med., **42**: 466–468, 1949.

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RESULTS OF PEDICLE TUBE-FLAP METHOD IN HYPOSPADIAS

DAVID M. DAVIS

In 1940 I published in *Surgery, Gynecology and Obstetrics* an article concerning the surgical treatment of hypospadias, in which I recommended a pedicle tube-graft or tube-flap placed in a subcutaneous tunnel.[1] Further communications, with some modification and amplifications of the method, were made in 1944,[2] 1947,[3] 1950[4] and 1951.[5]

A word on the theory of hypospadias operations would be appropriate at this point. All operations for this condition can be divided into two groups, namely, first, those in which the new urethra is constructed from the skin *in situ*, and then covered by suturing over it flaps of various kinds, and, second, those in which tubes of various kinds, composed of full-thickness or split-thickness skin, bladder or intestinal mucosa, or even segments of veins, are placed in subcutaneous tunnels. The great disadvantage of operations in the first group is that, unless the healing of the covering flaps is perfect, single or multiple fistulas occur, which are very hard to heal. The use of a subcutaneous tunnel prevents fistula formation but difficulties may occur by reason of necrosis of the grafts, contraction and stricturing of the new urethra, and the growth of hair within it.

After a good deal of none too-favorable experience with the Thiersch-Duplay *in situ* methods, the tunnelization methods seemed to me to offer promise of better things. Further, the most favorable material for the new urethra was undoubtedly the preputial skin, for the following reasons, first, it was close at hand, second, it was usually present in abundance, third, it was hairless, and fourth, if taken in full thickness it could be expected to grow with the penis. Others, particularly Van Hook, Charles Mayo and Hugh Young, had performed a few operations in which a pedicle tube flap of preputial skin had been made with its pedicle distal, that is, in the region of the coronary sulcus. Such pedicles, I soon found, invariably sloughed, usually, but not always, entailing the loss of the flap. One case in the series I am reporting today was operated on in this manner. The pedicle sloughed, but the tube miraculously survived, giving a most excellent result.

In the next operation the technique was changed in two particulars, namely, first, the flap was cut with the pedicle at the proximal end, and the subcutaneous tissue external to the tunica albuginea of the corpora cavernosa was included in it so that the natural blood supply of this area of skin was preserved, and second, the penis was bent double so that the full length of the tube flap could be drawn into the subcutaneous tunnel.

Read at annual meeting, American Urological Association, New York, N. Y. June 3, 1954.

[1] Davis, D. M.: Surg., Gynec. & Obst., 71: 790, 1940.

[2] Davis, D. M.: J. Urol., 52: 340, 1944.

[3] Davis, D. M.: In May's Reconstructive and Reparative Surgery. Philadelphia: F. A. Davis Co., 1947.

[4] Davis, D. M.: Plastic and Reconstructive Surg., 5: 373, 1950.

[5] Davis, D. M.: J. Urol., 65: 595, 1951.

TABLE 1

Type	Number	Finished	Unfinished	Awaiting Urethroplasty
Distal penile	1	1	—	—
Mid penile	8	7	1	—
Low penile	5	3	1	1
Penoscrotal	21	16	2	3
Anterior scrotal	5	5	—	—
Mid-scrotal	9	7	1	1
Perineal	2	2	—	—
Total	51	41	5	5

This method has proved most satisfactory. The tube flap never sloughs, a tube long enough to reach to the penoscrotal junction can usually be made, and the new meatus is at the tip of the glans where it belongs. The reconstruction can be finished at an early age, and numerous cases now have demonstrated that the new urethra grows with the penis.

Since this method was developed 51 cases of hypospadias have submitted themselves for operation, as shown in table 1. Of the five incomplete cases, three are awaiting operation for small single fistulas at the point of anastomosis between the old and new urethras, one has failed to return for financial reasons, and one has failed to return because he is in the Navy. His pinpoint penoscrotal fistula is so small that it was not noticed at his induction physical examination or later. In 5 cases the penis has been straightened, but it is not yet time for the construction of the new urethra.

Table 2 contains data concerning the ages of the patients.

As to the straightening operations, all but two have been done by the shawl-collar method described in previous publications. In one case, a wide urethra, probably due to an attempted Ombrédanne operation, was narrowed at the time of straightening. In another, posterior urethral valves were destroyed by electrocoagulation. In another, the only distal penile (or frenular) hypospadias in the series, the glans was tacked back dorsally and a ventral pedicle tube flap made at the same operation. This flap failed because of poor blood supply, and at a later date a dorsal pedicle tube flap made in the usual way gave a perfect result. In one perineal hypospadias the penis was straight, but lay subcutane-

TABLE 2

Age when first seen		Age at time of urethroplasty	
0–1 yr	6	4–5 yrs.	3
2–5 yrs.	17	5–6 yrs.	9
6–10 yrs.	11	6–7 yrs.	6
10–15 yrs.	4	7–8 yrs.	4
15–20 yrs.	6	8–10 yrs.	7
20 yrs. and up	7	10–15 yrs	4
		15–20 yrs.	5
		20 yrs. and up	8
Total	51	Total	46

TABLE 3

Type of operation		Cases
Pedicle tube flap in		43
Proximal pedicle	42	
Distal pedicle	1	
With Thiersch Duplay	19	
With Denis Browne	1	
Alone	23	
Thiersch Duplay only		2
Ventral tube flap		1
Total		46

ously The dorsal hairless skin was brought to the ventrum of the penis In a second perineal case, a small vagina was removed at the time of straightening In 2 cases the Nesbit method was used, once elsewhere and once by myself The Nesbit method, since it displaces the preputial skin to the ventrum of the penis, is not suited for use if the pedicle tube flap method of reconstruction is to be followed

Of the 41 finished cases, 38 are entirely satisfactory in that there are no fistulas, the urine is sterile and the voiding normal, with no dilatations or other treatment Three cases still require occasional dilatations

New urethras have been constructed in 46 cases (41 finished, 5 unfinished) The typical pedicle tube flap, with proximal pedicle, was used in 42 cases In one case, already mentioned, the pedicle was distal In one other case a tube flap was made from ventral penile skin to complete the glandular urethra In a third case all preputial skin had unfortunately been removed by a very radical circumcision This was the only case in which it was necessary to settle for a frenal meatus Other methods were used for part of the new urethra as shown in table 3

The 41 finished cases, some of which are shown photographically (figs 1, 2, 3),

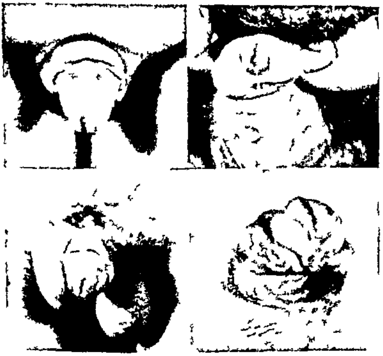

FIG 1 Views showing appearance of outer end of tube flap and its position at tip of glans

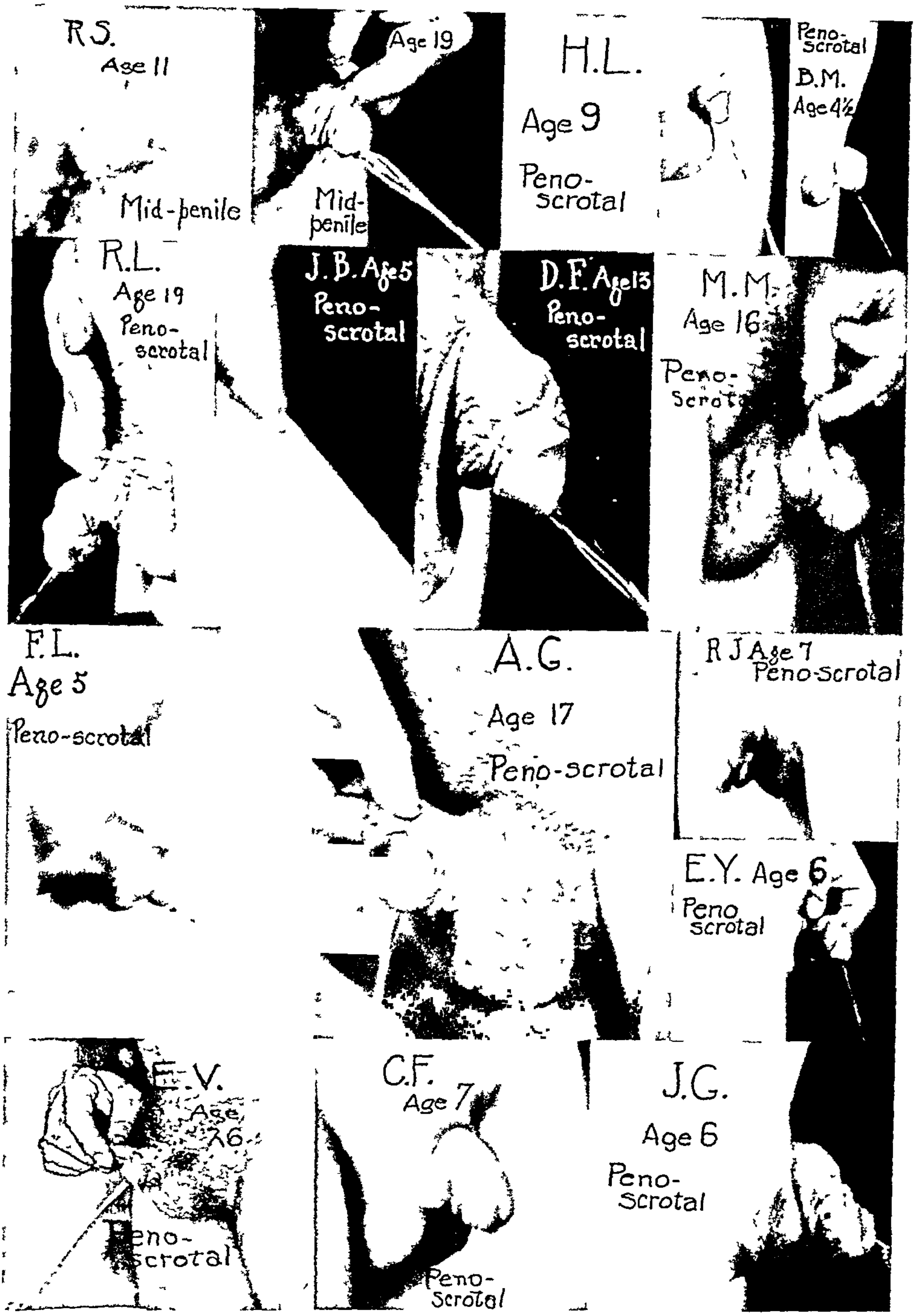

Fig. 2

represent, I believe, as nearly perfect results as it is possible to obtain. The meatus is at the tip of the glans in every case but one. In this case a glandular urethra was constructed, but the patient, a nervous, undisciplined boy, fingered the glans until the orifice was split back to the frenal region. I believe that the

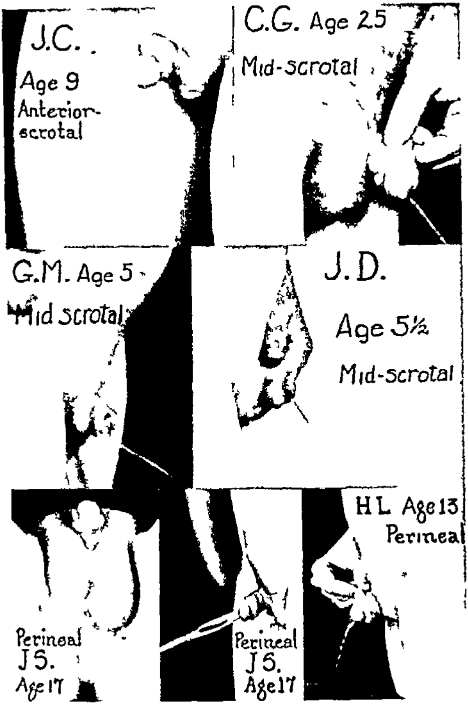

Fig 3

Table 4 *Total number of operations (including straightening)*

Operations	Cases
1	1
2	12*
3	16
4	3
5	4†
6	1
7	3‡
8	1§
Total	41

* In one case several straightening operations elsewhere failed because of urinary tract infection Then transurethral resection cure of infection Only two operations for construction of urethra

† Including one case of perineal hypospadias with suprapubic diversion and one case having three straightening operations

‡ Including one case of perineal hypospadias with suprapubic diversion

§ All prepuce had been removed at circumcision

TABLE 5. *Number of fistulas (after urethroplasty)*

Number	Cases	Closed	Not yet closed
None	22	22	—
One	19	14	5
Two	5	5	—
Total	46	41	5

TABLE 6. *Time elapsed since final operation in the 41 completed cases*

	Distal Penile	Mid Penile	Low Penile	Peno-Scrotal	Ant Scrotal	Mid Scrotal	Perin	Total
15–17 yrs.				2				2
10–15 yrs.		2	1	4		2	2	11
5–10 yrs.		2	1	6	3	2		14
1–5 yrs..	1	2	1	2		3		9
6 mos.–1 yr.		1		2				3
0–6 mos.					2			2
Total	1	7	3	16	5	7	2	41

3 cases requiring dilatation represent errors in technique on my part, in that the tube-flap was made too narrow.

Table 4 shows the number of operations performed in each of the 41 completed cases. The ideal number of operations is two—one for straightening the penis, and one for constructing the new urethra. With the pedicle tube flap method there can be but one fistula, namely, at the point of anastomosis of the old and new urethras. Fistulas when they occur are closed by the inversion technique previously described [1, 4].

Table 5 shows the number of fistulas actually occurring in the 46 cases in which new urethras have been constructed. In the 5 cases having two fistulas each, other methods were used in conjunction with the pedicle tube flap. All fistulas except five are now closed. Three of these will soon be due for closure, and in another the fistula is so small that the patient will not return. The fifth will not return for financial reasons.

Table 6 shows the time elapsed since completion. These unvarnished statistics show what actually happens in a series such as this. The outstanding feature is that there are no failures. Eight cases are still in process, two have failed to return. All others are complete.

The pedicle tube flap method has been used very successfully by Dodson of Richmond, Douglas of Nashville, and others, but some authors have brushed it aside as of no importance. This, I believe, is unjustified, and I present this series in an effort to demonstrate that the method is practical and reliable, and gives results which may be equalled, but not excelled.

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SECONDARY MALIGNANT INFILTRATION OF PENIS: REPORT OF FOUR CASES, TWO WITH SURGICAL TREATMENT FOR PALLIATION

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Secondary malignant invasion of the penis is a rare complication of neoplasms having their primary site elsewhere in the body and has, therefore, been reported infrequently. Thirty-four such cases appear in the literature; nine having the rectum as their primary site, eight from the urinary bladder, six from the kidney, seven from the prostate, three from the testes, one from the liver, and one from the lung.[1, 2, 3] The mode of transmission of these lesions is believed to be either through the venous system to the dorsal vein of the penis, or by the lymphatic channels that accompany the internal pudendal vessels, which form a link between the lymphatics of the penis and lower rectal area.

The outlook for patients undergoing radical surgery for cancer has improved since the advent of antibiotics and blood replacement therapy. This is shown in the overall statistics in such institutions as the John J. Jennings Institute where a decade ago the average mortality for such patients was 25 per cent; at present it has been reduced to 18 per cent. Patients with malignancies have an increased longevity so that the likelihood of distant metastases increases. The individual characteristics of neoplasms vary so widely that an attack on distant solitary metastatic lesions is sometimes justified. It is of interest that as recently as 1944, Wattenberg,[1] reporting on secondary carcinomas of the penis, concluded that the prognosis is unfavorable when these lesions occur. Metastases of any degree must be considered a serious prognostic finding. However, in the experience of Wattenberg, as these metastatic lesions were noted in the penis, a rapid demise was to be expected.

There are four previous cases reported elsewhere in which similar problems were treated surgically with symptomatic relief,[4, 5, 6, 7] and similarly two of our patients appear to be improved after amputation of the penis. In the case history

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Read at annual meeting, American Urological Association, New York, N. Y. June 3, 1954.

[1] Wattenberg, C. A. Unusual tumors and secondary carcinoma of the penis. J. Urol., 52: 169–175, 1944.

[2] Ney, C. Secondary carcinoma of the penis arising from carcinoma of the rectum. A. M. A. Arch. Surg., 65: 783–789, 1952.

[3] Melicow, M. M. and Ganem, E. J. Cancerous and precancerous lesions of the penis. J. Urol., 55: 486–515, 1946.

[4] Waller, J. I. and Hellwig, C. A. Metastases to corpora cavernosa from prostatic carcinoma. J. Urol., 69: 157–163, 1953.

[5] Cattell, R. B. and Mace, A. J. Metastases to the penis from carcinoma of the rectum. J. A. M. A., 146: 1230–1231, 1951.

[6] Boyd, H. L. Metastatic carcinoma of the penis secondary to carcinoma of the rectum. A review of the literature and report of a case. J. Urol., 71: 82–90, 1954.

[7] Niewiesch, H. Priaprismus be Primaren und Metastatischen Geschwulstein in den Schwelkorpen des Penis. Deutsche Ztschr. f. Chir., 241: 94–103, 1933.

presented by Waller and Hellwig,[4] a secondary neoplasm of the penis arising from a primary lesion in the prostate was excised and the patient was alive and apparently well 1 year after surgery. Cattell and Mace[5] reported the history of a patient with rectal carcinoma and metastases to the penis. He was examined and found to be free of metastases nine years after the amputation and eleven years after the original resection of the primary rectal carcinoma.

In the case history presented by Hobart L. Boyd,[6] the patient was alive and well 10 months after radical amputation of the penis. The patient reported by Niewiesch[7] has a penile lesion which was treated by simple amputation. Six months later there was a local recurrence and generalized metastases.

The diagnosis of a penile tumor is usually made by the patient or by the examining physician when there are complaints of urinary symptoms or of priapism. Painful priapism has appeared frequently in case reports of malignant infiltration of the corpora cavernosa. However, in the 4 patients observed by us, none had this complaint.

The following cases were treated on the New York State University Urological Service at the Kings County Hospital and are illustrative of this discussion.

CASE REPORTS

Case 1. A. C. (No. 27163), 68 years of age, white, with known carcinoma of the prostate of at least 2 years' duration, was being treated with 5 mg. stilbestrol, 3 times a day, but was admitted to the hospital because of severe urinary frequency and dysuria. No previous orchiectomy was performed. On examination, a hard, infiltrated mass on the dorsum of the penis was noted from the glans to the mid-

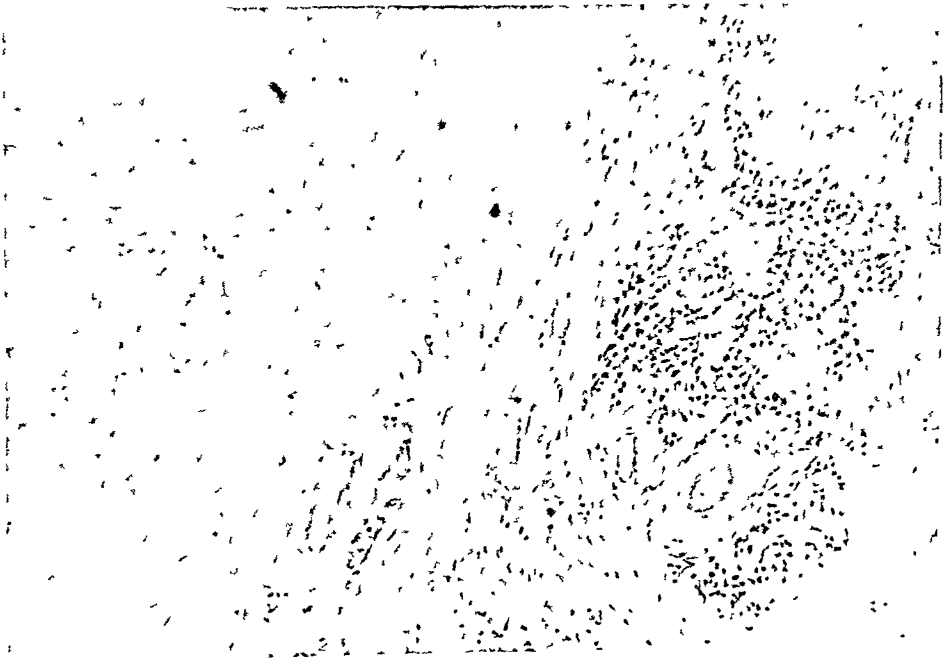

FIG. 1. Biopsy of penile nodule showing invasion of corpora cavernosa with scirrhous prostatic carcinoma.

shaft. At no time did the patient complain of priapism. Hospital studies did not reveal any bony metastases; acid phosphatase, 0.4 King-Armstrong units. A biopsy (fig. 1) was diagnostic for metastatic prostatic carcinoma. Treatment consisted of total amputation of the penis and orchiectomy. A search was made in the surgical specimen for any carcinomatous venous thrombi, but none were found. The dorsal veins of the penis did show phlebosclerosis. This patient made an uneventful recovery. It is now 10 months since the surgical procedure and at the patient's last visit to our clinic, he had no special complaints.

Case 2. P. F. (No. 35839), a 74-year-old white man, was seen in the out-patient department because of a firm tumor in the left testis. Preliminary studies in the hospital showed no other abnormal findings. X-rays of the chest and excretory urograms were interpreted as normal and the 17 keto-oxysteroids excreted were 9 mg. in 24 hours. The testis was excised through an inguinal incision with a high ligation of the spermatic cord. The excised testis contained a brown mass, 5 by 2 cm. The microscopic diagnosis was lymphosarcoma. Two months later, the patient was again admitted to the hospital because of an enlarged right inguinal node which was excised. The microscopic examinations showed metastatic lymphosarcoma similar in structure to the excised testis. Later, 4 months after the initial visit, the patient complained of another new growth. This time, an oval nodule was noticed on the glans penis (fig. 2). A biopsy (fig. 3) showed diffuse infiltration of the corpora cavernosa with lymphosarcoma. A partial amputation of the penis was performed without mishap and the patient has no complaints at present, ten months later.

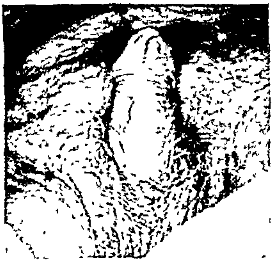

FIG. 2. Isolated nodule of metastatic lymphosarcoma at glans penis

Case 3. G. M. (No. 19582), a 64-year-old white man, was admitted to the ward in severe cardiac decompensation. In addition to his already serious complaints, he had marked difficulty of urination. Several months previously he suffered with intermittent attacks of hematuria. After aggressive treatment by the medical service, the patient's condition permitted cystoscopic examination. A bladder neoplasm, later proven to be squamous cell carcinoma, was noted on the right lateral wall. Excretory urograms demonstrated bilateral marked ureterectasis and caliectasis but it was deemed advisable to defer any immediate surgery. During his stay in the hospital, a hard nodule, 1 by 1.5 cm., was noted on the

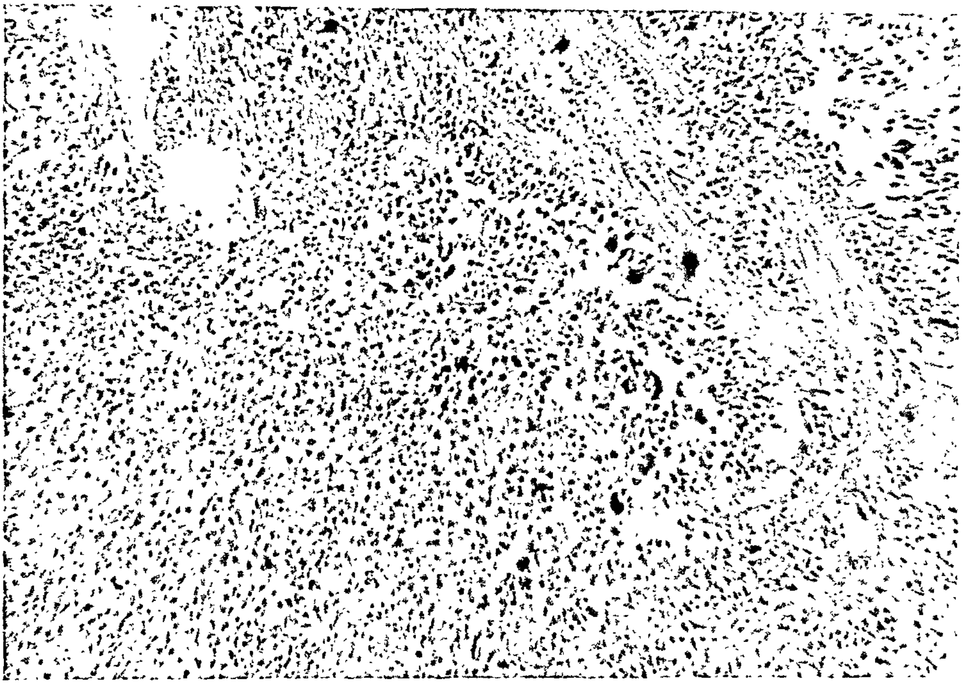

FIG. 3. Biopsy of nodule at glans penis showing diffuse invasion with lymphosarcoma

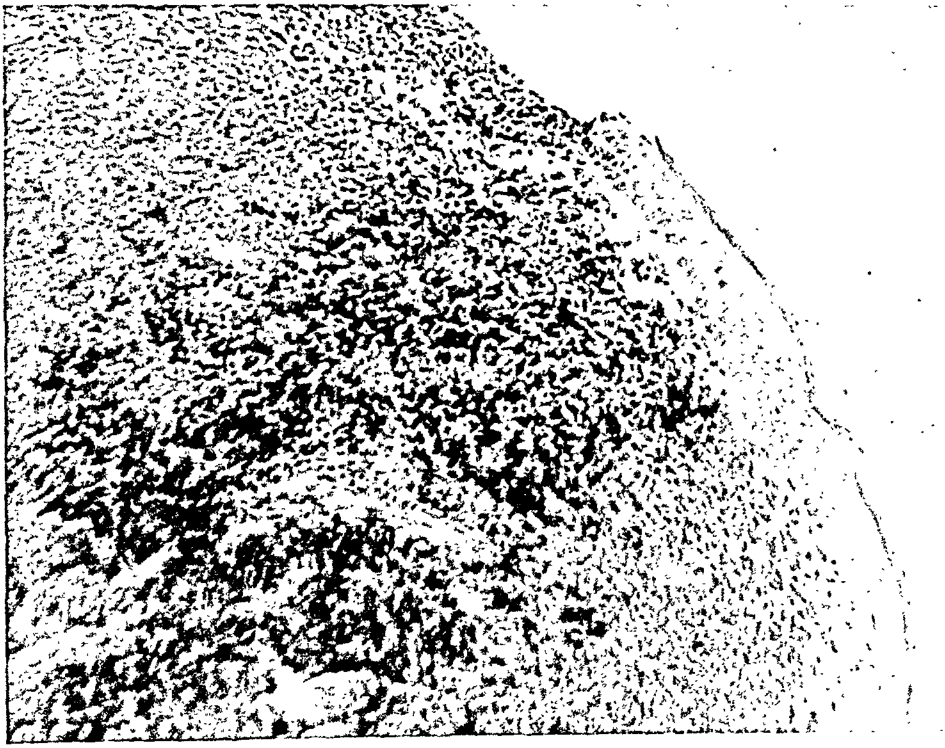

FIG. 4. Biopsy of penile lesion revealing invasion with metastatic carcinoma of bladder

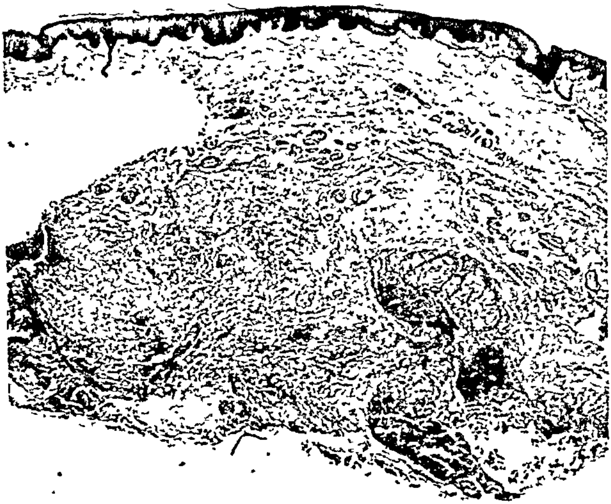

FIG 5 Biopsy of diffuse infiltration of corpora cavernosa with prostatic carcinoma showing nodules of hyperchromic carcinoma.

dorsal surface of the base of the penis. A biopsy (fig. 4) showed diffuse metastatic carcinoma in the corpora cavernosa. The penile lesion grew rapidly occluding the urethra. A palliative, bilateral, ureterocutaneous transplant was performed 1 month after the penile lesion was noted. In spite of this procedure, the patient continued on a septic course and expired 18 days postoperatively. Postmortem examination showed direct extension of the vesical neoplasm to the penis, rectum, and prostate, as well as metastatic pulmonary lesions. The pathologist noted marked anaplasia and rapidity of growth of this carcinoma.

Case 4. J. I. (No. 8467), a 55-year-old white man when first seen had been transferred from another hospital with a permanent cystotomy tube. Carcinoma of the prostate had been treated 3 years ago by transurethral resection, orchiectomy, and female sex hormones. The tissue removed was reported adenocarcinoma of the prostate. In spite of these measures, a spontaneous perforation of the urethra with urinary extravasation developed in November 1953, for which an emergency cystotomy was done. The clinical history has been reported in detail elsewhere.[8] Further studies disclosed a firm, impassable infiltration of the base of the penis occluding the urethra. Bone studies showed osteolytic and osteoblastic metastases to the left ischium. The acid phosphatase was 4.7 King-Armstrong units and the 17 ketosteroids in the 24-hour urine were 5.1 mg. Because of the intractable bone pain and the appearance of lymphedema of the left leg, in addition to stilbestrol, cortisone, 100 mg. a day, was started with marked palliation.

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[8] Herman, H and Kook, H · Secondary carcinoma of the penis To be published, read in part at the Brooklyn Urological Society, April 7, 1954.

The patient was then transferred to Kings County Hospital for further treatment, and the findings previously reported were corroborated, the acid phosphatase was now 1.5 King-Armstrong units and the 17 keto-oxysteroids were 5.1 mg. in the 24-hour urine. The patient required 100 mg. of cortisone a day for relief of pain. Physical examination disclosed the entire shaft of the penis to be diffusely edematous and infiltrated with firm plaques. A biopsy (fig. 5) disclosed diffuse anaplastic carcinomatous invasion of the corpora cavernosa. Because of involvement of the posterior urethra with carcinomatous infiltration, it was decided to leave the cystotomy tube in situ. It was felt that this was a case of direct extension of the prostatic carcinoma to the urethra and then retrograde lymphatic or venous spread to the corpora cavernosa. The patient has never complained of priapism. He expired suddenly 4 months after admission of acute coronary artery disease.

SUMMARY

Four additional cases of metastatic carcinoma of the corpora cavernosa in patients with primary cancer of the bladder, prostate, and lymphosarcoma of the testis are reported. This brings a total number of such reported cases to thirty-eight.

In the case of two of our 4 patients, surgical excision of the lesions have resulted in at least temporary relief. Two patients are living 10 months after surgery.

None of our patients complained of priapism. This symptom is not necessarily a part of the syndrome that occurs with malignant infiltration of the penis.

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CELLULAR CHANGES FROM GRADED TESTICULAR ISCHEMIA

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The cellular elements of the testis are known to vary in their resistance to temperature change, to chemicals, and to certain hormones. Cytologic changes after different periods of ischemia have been incompletely studied, yet such a study would tell us much regarding the effects of torsion of the testis.

EXPERIMENTAL METHOD

An experiment was designed to create complete testicular ischemia for varying intervals of time. The effect of this trauma on different cellular elements of the testis was then histologically determined.

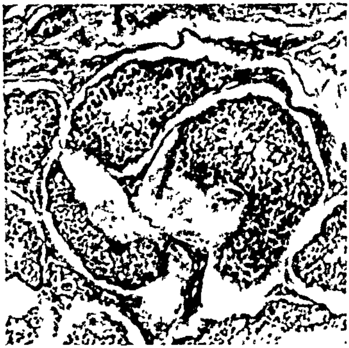

FIG. 1. Normal testis. *a*, Active spermatogenesis. *b*, Leydig cells. *c*, Basement membrane.

Experimental ischemia was applied to thirty-three separate testes of unselected male mongrel dogs. Several older dogs were included because they were available.

Under veterinary nembutal anesthesia, the genital region was prepared and draped. A 4 cm. incision was made over the external inguinal ring, through which the testis and cord were freed completely from the surrounding tissues. A testicular biopsy was made through a stab wound in the tunica albuginea (fig. 1). A soft, latex, 18F catheter was placed as a tourniquet about the cord just distal to the external ring, and brought out through a separate short incision (fig. 2). Care was taken to avoid damaging the cord structures. The tourniquet was tightened, and clamped when arteriolar bleeding from the biopsy site just ceased. The wound was closed in layers with No. 60 cotton. A towel securely wrapped about the dog's abdomen prevented removal of the clamp. The tourniquet was removed

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Read at annual meeting, Western Section of American Urological Association, Victoria, B. C. April 19–22, 1954.

Note by editor. Dr. Smith's paper received honorable mention in the Joseph F. McCarthy Prize Essay Competition sponsored annually by the Western Section.

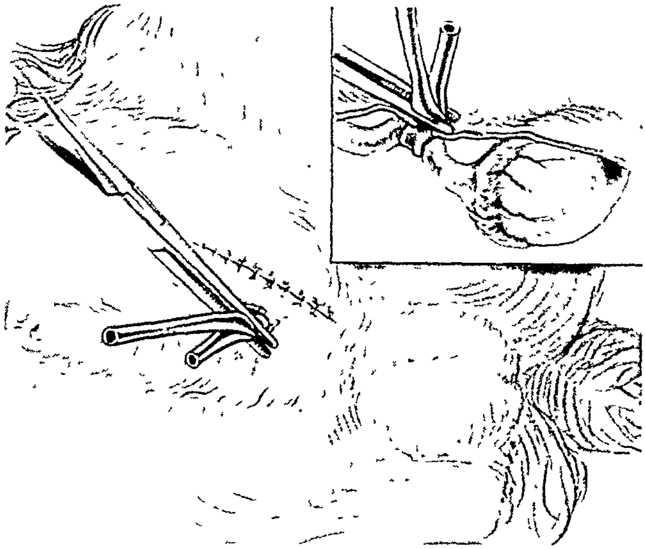

FIG. 2. Experimental method: Latex catheter encircles cord structures at external ring. Clamp holds tourniquet at proper tension. Both are brought out through separate stab wound.

after varying periods of ischemia, up to 14 hours, had elapsed. Sixty days later a scrotal incision was made to excise the affected testis.

RESULTS OF EXPERIMENTAL ISCHEMIA (TABLE 1)

Two hours (4 testes). (See figure 3.) Spermatogenesis was slightly depressed in all but one of 4 testes after ischemia of 2 hours' duration. This was seen in the loss of the more mature forms. The Sertoli and Leydig cells showed no change. The viability and thickness of the basement membrane remained the same. Certain general effects of ischemia were noted. Testis 11-R showed a fibrinoid change in the muscular walls of the arterioles with lymphocytic infiltration. Testis 57-R showed slight vacuolar degeneration of all the cellular elements. The epididymides were unchanged except for a slight increase in intertubular fibrosis in specimen 160-L.

Four hours (3 testes). (See figure 4.) Ischemia for 4 hours was the critical period for major damage to the testicular elements. All spermatogenic and Sertoli cells were destroyed in one testis, 150-L. The other representative testis, 186-R, showed only a rare peripheral tubule containing Sertoli cells, but with depressed spermatogenesis. The Leydig cells were absent in the center of the testis and formed a solid viable margin beneath the thickened, slightly fibrosed tunica albuginea. They appeared in clumps but in apparently normal total numbers.

Testis 150-L had a fibrotic center containing many pigment-filled phagocytes. Testis 165-R degenerated entirely within several weeks after operation, undoubtedly because of vascular thrombosis at the time of surgery.

Both remaining epididymides showed an increase in intertubular fibrosis. The epithelium remained essentially unchanged.

Six hours (4 testes.) (See figure 5.) All spermatogenic and Sertoli cells were eliminated by 6 hours of ischemia. Not even the viable margin of tubules seen in

TABLE 1. *Results of experimental ischemia*

	Spermatogenesis		Leydig cells	Basement Membrane	Comments
	Before Ischemia	After Ischemia			
2 hr					
11 R	++++	++++	No change	No change	
160 L	+++	++	No change	No change	
2 R	+	±	No change	No change	Some hyaline material in tubules
57 R	±	0	No change	No change	Vacuolar degeneration
4 hr					
150 L	++++	0	Margin about testis	Mostly intact	Some central fibrosis
165 R	++++				Sloughed 2 weeks after surgery
186 R	+++	±	Margin about testis	Intact	
6 hr					
166 R	+++	0	0	Intact	Mild diffuse fibrosis
160 R	++	0	Margin about testis	Intact	Septal fibrosis
40 R	++++				Sloughed 2 weeks after surgery
8 R	+	0	0	Intact	Mild diffuse degeneration
8 hr					
11 L	+++	0	Few marginal groups	Many intact	Diffuse intra- & extratubular fibrosis. Central infarction
180 R	+++	0	Few marginal groups	Many intact	Diffuse intra- & extratubular fibrosis Many macrophages
58 L	++++	0	0	Occasional one intact	" "
79 R	±	0	0	Occasional one intact	" "
180 L	?	0	0	Intact	Diffuse intra- & extratubular fibrosis Some perivasculitis
2 L	++++	0	0	None identified	Complete degeneration
40 L	++++	0	Few marginal groups	Intact	Diffuse intra- & extratubular fibrosis
10 hr					
174 R	++++	0	0	0	Diffuse fibrosis
166 L	++++	0	0	0	Diffuse fibrosis
174 L	++++	0	0	0	Diffuse fibrosis
58 R	+	0	0	Occasional one intact	Diffuse fibrosis

TABLE 1—*Continued*

	Spermatogenesis		Leydig cells	Basement Membrane	Comments
	Before Ischemia	After Ischemia			
12 hr					
85 R	++++	0	0	0	Diffuse fibrosis
57 L	++++	0	0	Occasional one intact	Diffuse fibrosis
89 R	++++				Sloughed 2 weeks after surgery
85 L	?	0	0	Occasional one intact	Diffuse fibrosis
186 L	++++	0	0	0	Diffuse fibrosis
89 L	++++				Sloughed 2 weeks after surgery
165 L	++	0	0	0	Diffuse fibrosis
14 hr					
79 L	±	0	0	Occasional one intact about periphery	Diffuse fibrosis, central hyalinized mass
137 R	++++				Sloughed 2 weeks after surgery

testes after 4 hours of ischemia could be found after careful search. Two testes, 166-R and 8-R, showed a complete absence of Leydig cells. Testis 160-R showed a small viable margin about the periphery. The basement membrane was intact in all specimens and showed no secondary thickening. Many pigment-filled macrophages were found in the center of all specimens. Moderate fibrosis of the septa was present in 160-R, and 8-R showed diffuse degenerative change.

All viable specimens showed definite epididymal changes consisting of slight intertubular fibrosis, cystic dilatation of the tubules, and a flattened single layer of tubular epithelium.

Testis 40-R degenerated entirely within three weeks after operation, undoubtedly from vascular thrombosis at the time of surgery.

Eight hours (*7 testes*). (See figure 6.) This period of ischemia caused the complete degeneration of spermatogenic and Sertoli cells. None were found on any of the sections. The Leydig cells were absent in all but three of the testes, 11-L, 180-R, and 40-L. These had a few scattered peripheral groups beneath the tunica albuginea.

The basement membrane of the tubules showed irregular degeneration, but occasionally was intact, particularly at the periphery. In addition, there was a diffuse fibrosis, both within the tubules and throughout the testis. The tunica albuginea was greatly thickened and fibrosed. One specimen, 11-L, showed central infarction. Diffuse degenerative changes with many pigment-filled macrophages, particularly in the center, were found in all the specimens.

Three epididymides in this group, 180-R, 2-L, and 40-L, showed cystic dilatation of the tubules, mild intertubular fibrosis, and a flattened single layer of tubular epithelium. Four epididymides, 11-L, 58-L, 79-R, and 180-L, developed

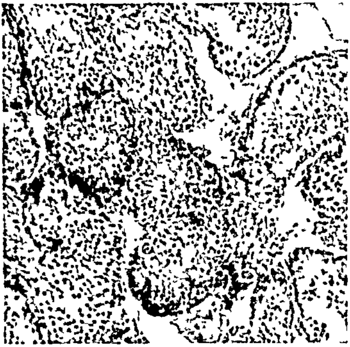

FIG. 3. Testis 160-L after 2 hours' ischemia. *a*, Impaired spermatogenesis. *b*, Normal Leydig cells. *c*, Basement membrane.

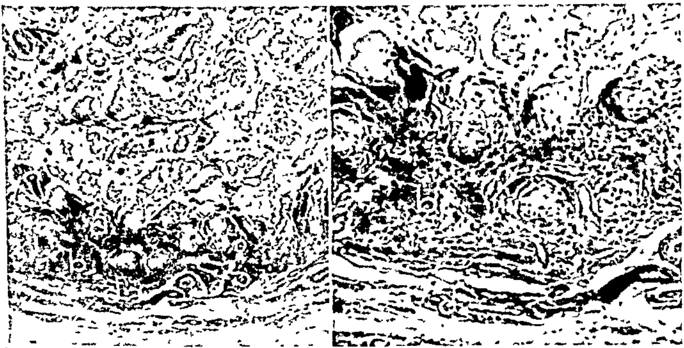

FIG. 4. Testis 150-L after 4 hours' ischemia. *a*, No remaining spermatogenic cells. *b*, Clumped Leydig cells about periphery. *c*, Basement membrane. *d*, Tunica albuginea.

severe intertubular fibrosis with small tubules lined with several layers of nonciliated epithelium.

Ten hours (4 testes). (See figure 7.) Ischemia of 10 hours' duration caused a complete degeneration of spermatogenic, Sertoli and Leydig cells. The basement membranes were absent with the exception of a rare tubular outline about the periphery in 58-R. Diffuse fibrosis with many pigment-filled macrophages was present in all specimens.

No epididymides were seen in any of the specimens.

Twelve hours (7 testes). The spermatogenic, Sertoli and Leydig cells were absent in all of these specimens. A rare basement membrane was found about the periphery in specimens 57-L and 85-L; otherwise diffuse fibrotic replacement of the testes had taken place. Many pigment-filled macrophages were present. Testes 89-R and 89-L degenerated entirely within several weeks of operation, from vascular damage by the tourniquet.

Two specimens, 85-R and 165-L, showed cystic dilatation of the epididymal

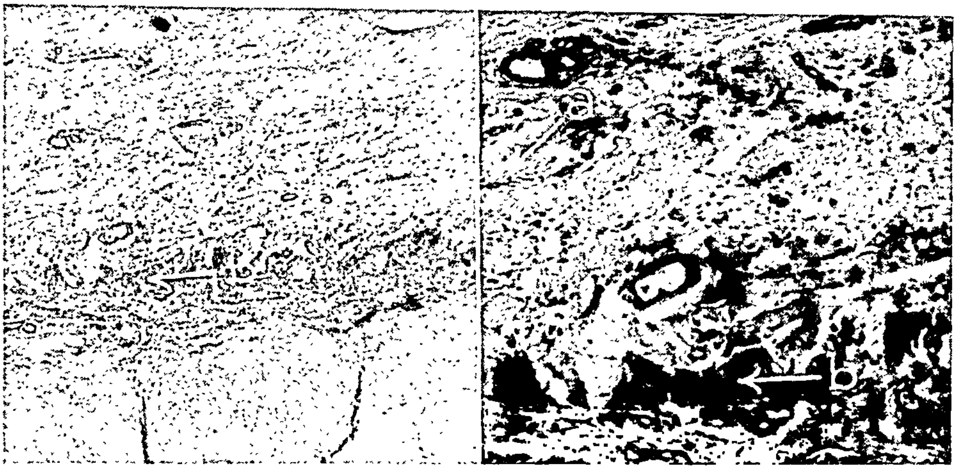

FIG. 5. Testis 160-R after 6 hours' ischemia. *a*, No remaining spermatogenic cells. *b*, Thin layer clumped Leydig cells about periphery. *c*, Basement membrane with early fibrosis.

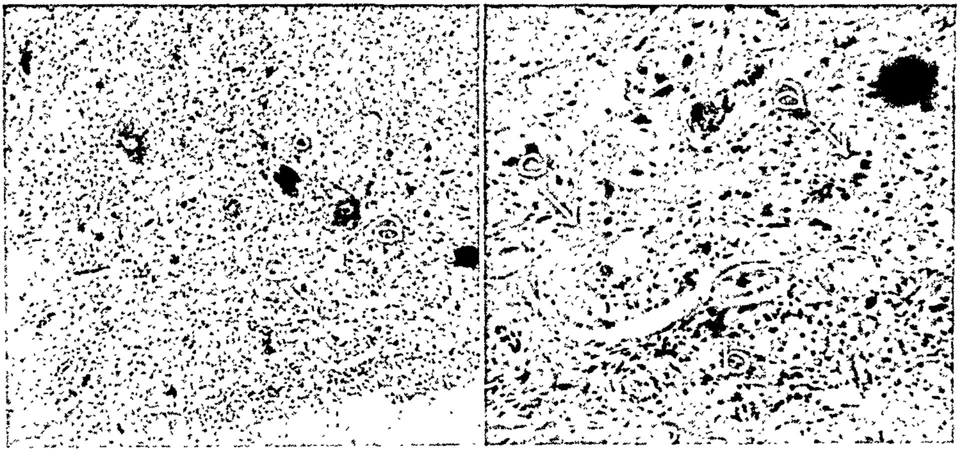

FIG. 6. Testis 180-R after 8 hours' ischemia. *a*, No remaining spermatogenic cells. *b*, Occasional small clump of Leydig cells about periphery. *c*, Basement membrane with marked intra- and extratubular fibrosis. *d*, Fibrotic tunica albuginea.

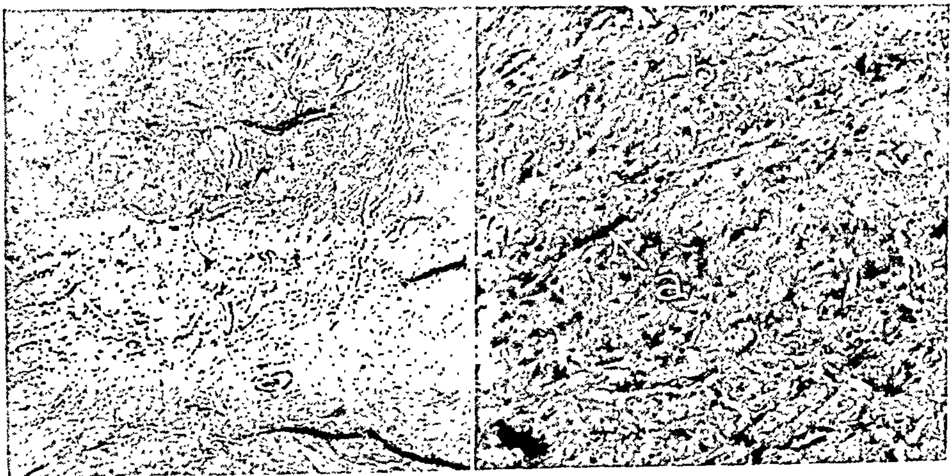

FIG. 7. Testis 174-R after 10 hours' ischemia. *a*, Shadow of basement membrane. *b*, Diffuse fibrosis.

tubules with marked intertubular fibrosis and a single layer of flattened tubular epithelium In specimens 85-L and 186-L there was severe intertubular fibrosis with small tubules lined by several layers of nonciliated epithelium The remaining epididymides were not found on the final specimen

Fourteen hours (2 testes) Dense fibrosis was present in 79-L, with a rare basement membrane remaining peripherally The central hyalinized mass contained many pigment-filled macrophages Testis 137-R degenerated entirely within several weeks of operation, so that no epididymal structures could be found on the final specimen

DISCUSSION

The effects of testicular ischemia are of considerable interest because of their application to clinical torsion of the testis Experimental ischemia is admittedly not directly comparable to clinical torsion, since the vascular changes with torsion in the human being may vary from partial venous obstruction to complete arterial occlusion These experiments, however, were designed to show the effect of complete testicular ischemia in dogs, and so would show the effects of the most extreme testicular torsion

Maatz[1] applied tourniquet compression to the spermatic cords of 45 rats He had irregular results because of vascular thrombosis, but found that with ischemia of 8 hours' duration spermatogenic cells were eliminated but the Sertoli and Leydig cells remained He found that mature spermatogenic cells were the most sensitive The spermatogonia were the least sensitive and were the last to be eliminated He mentioned that some spermatogenic elements survived the 8 hour period of ischemia

Hellner[2] quotes Enderlen, who states that testicular regeneration can occur if ischemia is applied for 16 hours Complete degeneration occurs after 24 hours of ischemia Hellner occluded all spermatic cord vessels on dogs for periods ranging from 4 to 72 hours Only 1 dog was used for each time interval He found complete atrophy of all testicular cells after 7 hours of ischemia

Iwasita[3] obstructed the vessels of the spermatic cord in 8 human subjects who had tuberculous epididymitis The testes and epididymides were removed 1 month later He found little testicular damage after 5 hours of ischemia, partial necrosis after 10 hours, and complete hemorrhagic necrosis after 15 to 24 hours

These older experiments used different species and different techniques, which account for the reported discrepancies in the effects of ischemia on the cellular elements of the testis

The results of the present experiments were fairly uniform After a critical period of 4 hours of ischemia there was a complete loss of spermatogenic cells

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[1] Maatz, R Anatomic changes following temporary circulatory strangulation of the testis Centralbl f allg Path u path Anat , 59: 243, 1934

[2] Hellner, H Local circulatory disturbances Beitr z klin Chir , 158 225, 1933

[3] Iwasita, K Local circulatory disorders of testicles, clinical and experimental study of effect of occlusion of spermatic cord vessels, with special consideration of torsion of testicle Jap J Dermat & Urol , 45: 126 1939

In the 4 to 8 hour interval of ischemia, the Leydig cells remained fairly viable and curiously formed a margin of tightly packed groups beneath the tunica albuginea. This margin was thin and its thickness varied considerably in the 8 hour group. It is difficult to explain this margin of Leydig cells about the periphery. Destruction of the other testicular elements, of course, caused closer grouping of the remaining cells. The available blood supply would be better in this subtunical area since the arterial supply of the testicular parenchyma originates beneath the tunica albuginea.[4] An increase in the interstitial cell stimulating hormone (ICSH) could occur because of severe damage to both testes; however, this margin was noted in two testes having essentially normal scrotal partners (160-R and 11-L).

Ten or more hours of ischemia resulted in the elimination of all Leydig cells and all but a rare basement membrane. The testicular elements were replaced by diffuse fibrosis

Thrombosis at the time of application of the tourniquet was apparently responsible for the loss of a few testes, which became necrotic and sloughed several weeks later. Thrombosis probably did not play a significant role in the damage to the rest of the testes as the effects were similar within each ischemic group.

SUMMARY AND CONCLUSIONS

The testes of 33 dogs were subjected to periods of ischemia ranging from 2 to 14 hours.

The spermatogenic cells were slightly damaged by 2 hours, severely injured by 4 hours, and eliminated by 6 hours of ischemia.

The Leydig cells were severely damaged by 8 hours of ischemia and eliminated by 10 hours.

Ten hours or more of ischemia resulted in nearly complete fibrotic replacement of the testes.

The author acknowledges with appreciation the inspiration and assistance of Dr. Frank Hinman, Jr. in this project and also thanks Dr. Gerald M. Miller, Mr. Rudolph Skarda, Mr. Charles Aiello, and Mr Russell Reddick for their suggestions and help.

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[4] Paul, M.: The blood and lymph pathways in the spermatic cord (with particular reference to their applied anatomy and pathology). Ann. Roy. Coll. Surg. Eng., 7: 128, 1950.

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TUMORS OF THE TESTIS

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This study is based upon 50 cases of malignant testicular tumors treated at the Veterans Administration Medical Teaching Group Hospital (Kennedy), Memphis, Tennessee from 1947 through 1953 We were impressed with the unusually high number of cases seen during this 6-year period and encouraged by the comparatively good results obtained We were also aware of the paucity of reports in the literature of the treatment of testicular tumors by million volt x-ray therapy These factors prompted us to initiate this study

The general population is not represented by these cases since they were selected from the veteran population exclusively A small number (eighteen) of the patients had orchiectomy prior to transfer to this hospital for further therapy while only 2 patients were given follow-up care alone at this institution Any figures or incidence would not be truly representative since some of the cases were discovered from admissions to other hospitals before transfer to this hospital Forty-six, or 92 per cent, of the patients were white and four, or 8 per cent, were Negroes The average age was 32 6, ranging from 20 to 55 years Thirty of the patients, or 60 per cent, were between 26 and 34 years of age These figures agree closely with those of Culp,[1] Sauer et al ,[2] and Nesbit et al[3] Seminomas occurred in an older age group, 35 years average, with two tumors occurring in 55 year-old patients The ages of those with embryonal carcinoma averaged 32 2 years while teratocarcinoma was found in the youngest group, 28 years average O'Connell and Geschickter[4] found a similar trend in age distribution with respect to the types of tumors The figures show that testicular tumors have their greatest incidence in young adulthood after sexual maturity

The left testis was involved in 26 cases (52 per cent) and the right in 22 cases (44 per cent) This observation is the reverse of the figures presented by Sauer, Watson and Burke[2] and Nesbit and Lynn[3] who found the right testicle more frequently involved

Two cases of bilateral tumors were found in this study The incidence of bilateral testicular tumors in 7000 cases collected by Gilbert and Hamilton[5] was 2 per cent We wish to give special consideration to these 2 cases because of their rarity One of these 2 cases of bilateral tumor occurred concomitantly

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Read at annual meeting, American Urological Association, New York, N Y June 2, 1954

[1] Culp, D A Testicular neoplasms, an analysis of 113 cases J Urol , 70 282–295, 1953

[2] Sauer H R , Watson, E M and Burke, E M Tumors of the testicle Surg , Gynec & Obst , 86 591–603, 1948

[3] Nesbit, R M and Lynn, J M Malignant testicular neoplasms Surgery, 20 273–279, 1946

[4] O'Connell, H V and Geschickter, C F Tumors of the testes U S Armed Forces M J , 1: 719–732, 1950

[5] Gilbert, J B and Hamilton, J B Studies in malignant testis tumors Surg , Gynec & Obst , 71: 731–743, 1940

Hotchkiss and Laury[6] reviewed the literature from 1805 to 1949 and collected 21 records of men having normally located testicles with proven cancer present in each at the same time. They added a case of their own which was diagnosed as bilateral reticulum cell sarcoma. Gill and Howell[7] collected 155 cases of bilateral malignancy and added a case of their own with concomitant bilateral embryonal carcinomas. Correa Fuenzalida and Raventos[8] in 1947 reported 4 cases of bilateral tumors, three of which occurred concomitantly. In the same year Turkel and Migliaccio[9] presented a case of concomitant seminomas. Gürsel[10] (1951) reported a case of concomitant bilateral sarcoma of the testicles. The first American case of concomitant bilateral interstitial cell tumor was recorded by Garvey and Daniel[11] in 1951. The addition of the following case brings the recorded total number of concomitant bilateral testicular tumors to thirty. Others may be buried in the many papers on testicular tumors.

C. W., No. 26744, a 29-year-old Negro, was admitted complaining of enlargement of both testicles and pain in the left flank and the left costovertebral angle. The right testicle had been enlarging for 6 weeks prior to admission and the left for 5 weeks. There was no pain in the testes or history of trauma. Physical examination revealed extremely hard testicles about the size of large lemons. There was marked bilateral inguinal and subinguinal lymph node enlargement with perineal and perirectal induration. The left axillary lymph nodes were enlarged and hard.

Chest x-ray and osseous survey were negative. An excretory urogram revealed a nonfunctioning left kidney. A Friedman test was negative. Bilateral orchiectomy was performed on March 15, 1949. A pathological diagnosis of embryonal carcinoma was made and the patient started on deep x-ray therapy as a palliative measure, since metastatic spread was extensive. There was moderate reduction of pain in the left flank following x-ray therapy. Intestinal obstruction forced a transverse colostomy on April 5, 1949 and radiation therapy was discontinued. The rapidly deteriorating course was accelerated by the development of pleural effusion and terminated in a respiratory death 46 days after admission. Postmortem examination revealed metastases of the embryonal carcinoma to the left lung, heart, spleen, liver, pancreas, bladder, ureters, prostate and gastro-intestinal tract. Lymph nodes of the mediastinum, mesentery and left inguinal regions were involved. The tumor had produced bilateral hydronephrosis, hydroureter and obstruction of the rectum.

The second case of bilateral cancer of the testicle was not concomitant. Nevertheless, it was unusual because the patient was a pseudohermaphrodite and had bilateral cryptorchidism. Gilbert[12] collected 60 cases of testicular tumors in pseudohermaphrodites from the literature and added a case of his own. There were 8 cases of bilateral testicular tumors among this series of 60 pseudohermaphrodites. This cases brings the total to 9 cases.

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[6] Hotchkiss, R. S. and Laury, R. B.: Concomitant bilateral malignant testicular tumors. J. Urol., **63:** 1086–1092, 1950.

[7] Gill, R. D. and Howell, R. B.: Primary bilateral testicular tumor. J. Urol., **59:** 940–947, 1948.

[8] Correa Fuenzalida, O. and Raventos B. E.: Tumores bilaterales del testiculo. Bol. Soc. cir. Chile, **25:** 212–214, 1947.

[9] Turkel, E. F. and Migliaccio, A. V.: Bilateral testicular seminoma. Urol. & Cutan. Rev., **51:** 42–46, 1947.

[10] Gürsel, A. E.: Sarcome bilateral du testicule. J. urol., Paris, **57:** 82–87, 1951.

[11] Garvey, F. K. and Daniel, T. B.: Bilateral interstitial cell tumor of the testicle. J. Urol., **66:** 713–719, 1951.

V C. B., No. 77190, a 31-year-old white male farmer, was admitted with a history of bilateral undescended testicles until 6 weeks prior to admission when he noted a "knot" in his right scrotum. A right orchiectomy was advised and performed 2 weeks before admission to this hospital. The pathological diagnosis was seminoma. Examination on admission revealed a recent scrotal scar and surgical absence of the right testicle. A nodular left testicle was palpated. The patient stated that the left testicle had descended into the scrotum since his right orchiectomy. The external genitalia were pseudohermaphroditic. A small, short penis was present, resembling a hypertrophied clitoris. Chest x-ray and retrograde pyelograms were within normal limits. A left orchiectomy was done on May 18, 1949. The postoperative course was uneventful. The pathological diagnosis was seminoma. The course of deep x-ray therapy to the lymphatic drainage was interrupted on several occasions because of irradiation anemia and leukopenia. He received a total tumor dose of 400 r before his discharge. On February 2, 1950 there was no evidence of metastasis on chest x-ray films and no deviation of the ureters on the excretory pyelograms. The patient was found to be severely anemic and multiple whole blood transfusions were given along with testosterone and iron.

On December 1, 1950 the anemia had improved and no evidence of recurrence of the tumor could be found. He was rechecked in September 1951, October 1952 and November 1953 and there was no evidence of recurrence or metastatic spread of the seminoma. The patient is living and well four and a half years following bilateral orchiectomy. He denied ever having had sexual intercourse or a desire for it.

There is an apparent association between pseudohermaphrodism and cryptorchidism. This is shown by Gilbert and Hamilton[5] who found that in a series of 345 abdominal testicular tumors, 11 per cent were pseudohermaphrodites.

It is not understood whether the ectopic location of the testicle predisposes to malignancy or other factors, such as hormones, which cause the maldescent, are the same factors which produce future malignancy. Whatever the cause, it has long been recognized that ectopic testicles become malignant more frequently than normally located ones.

Our findings agree with those of Lewis[13] and Gilbert[12] that orchiopexy or spontaneous descent has no lessening influence on the development of tumors in the cryptorchid. One of our patients had a right cryptorchid testicle until puberty when it descended spontaneously. A seminoma developed in the right testicle at the age of 51 years.

Kaplan and Roswit[14] presented a case of bilateral involvement in a patient who had a bilateral orchiopexy at 14 years of age. Twenty-seven years af orchiopexy a seminomatous right testicle was removed and 4 years later a tera carcinomatous left testicle was resected.

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[12] Gilbert, J. B. Studies in malignant testis tumors. J. Urol., 48: 665-672, 1942.

[13] Lewis, L. G. Testis tumors. J. Urol., 59: 763-772, 1948.

[14] Kaplan, G. and Roswit, B. Bilateral testicular tumors following bilateral orchiopexy. J. A. M. A., 144: 1557-1558, 1950.

Gill and Howell[7] believe that the chance of the remaining normal testis coming malignant, after having one malignant testis removed, is 770 times great as the incidence of cancer in either testis in the general population. I this reason the follow-up care of a patient who has been treated for testicu cancer should include careful observation of the remaining testicle.

Four patients in this series had unilateral or bilateral cryptorchidism at so time. Two of the four patients had unilateral abdominal cryptorchid testes a were admitted because of acute abdominal pain. Surgery revealed torsion seminomatous abdominal testes in both patients. A barium enema may outli an abdominal cryptorchid testis as a space-occupying mass. The incidence seminoma in cryptorchid testicles is brought out by Lewis[13] who found 12 of tumors in cryptorchids to be seminomas. All four of our patients with cry orchidism had seminomas.

Two cases were found in which the tumor developed in a normally descend left testicle while on the right side there was an abdominal cryptorchid. Gilb and Hamilton[5] reported 23 similar cases in their series of unilateral cryptorchi This represents a small percentage however, since they found in the same ser that the tumor occurred in the ectopic testicle in 97.5 per cent of the patie with unilateral cryptorchids.

In one of these 2 cases, the patient had bilateral gynecomastia and a po tive Friedman test on admission. A diagnosis of malignant teratoma was ma following orchiectomy. The descended testicle had been replaced by tum tissue which had undergone degeneration, fibrosis and necrosis (fig. 1). It w difficult to find enough tumor tissue to make a microscopic diagnosis. We belie that the gynecoid changes in this patient represent the "castration effect" c

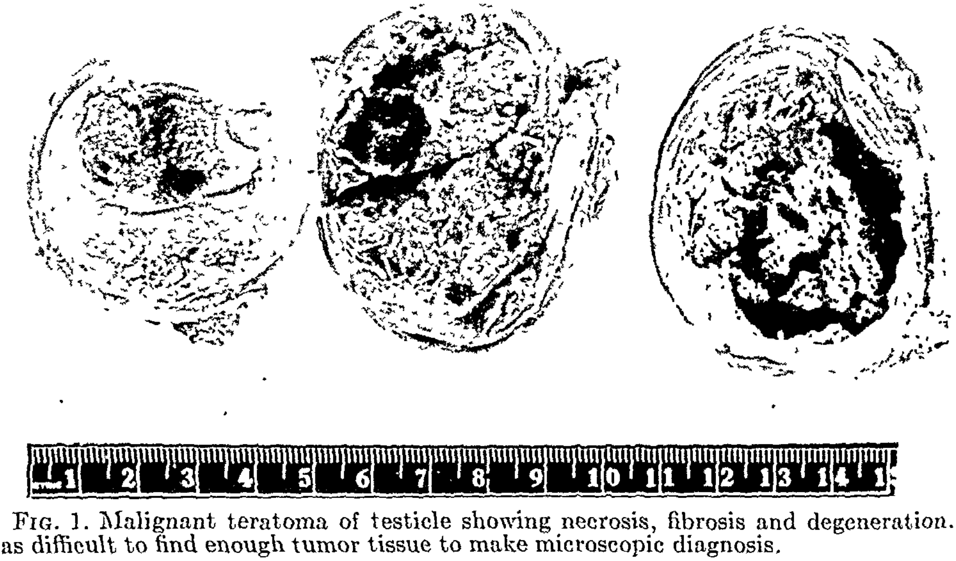

FIG. 1. Malignant teratoma of testicle showing necrosis, fibrosis and degeneration. was difficult to find enough tumor tissue to make microscopic diagnosis.

TABLE 1 *Types of tumors*

Types	Number	Per cent
Seminoma	21	48%
Embryonal carcinoma	16	32%
Teratocarcinoma	9	18%
Unlisted	1	2%
Total	50	100%

scribed by Vermooten and Hettler.[15] In the second case the patient had a positive Friedman test before treatment. The testicle was removed and proved to be embryonal carcinoma with chorio-epitheliomatous elements After completion of deep x-ray therapy, the Friedman test was negative. No metastatic deposits could be found on admission or on re-examination 6 months later. The Friedman test was done 27 times in this series. It was positive 6 times and negative 20 times. There was one questionable test. It is felt that the test was of little or no diagnostic aid since no pure chorio-epitheliomas were found in the group.

The pathological classification of testicular tumors is a controversial subject. The work of Dixon and Moore[16] and O'Connell and Geschickter[4] has aided greatly in clarifying the problem.

Moore[17] describes four basic types of cells: the adult teratoma, seminoma, embryonal carcinoma and choriocarcinoma. Tumors may be composed of one of these cell types or they may be composed of a complex combination of any two or more of them.

The tumors in this series fell into three groups: 1) seminoma, 2) embryonal carcinoma and 3) teratocarcinoma There were no pure choriocarcinomas found in this study. Adult or mature teratomas were combined with malignant or teratocarcinomas because both are potentially malignant since they may have other types of cells present and are therefore to be considered as malignant as the most malignant cell present. O'Connell and Geschickter[4] doubted the value of subdividing teratocarcinomas for the same reason.

One case was unclassified. The slides from this tumor were not available for review Table 1 shows the number and percentage of each type of tumor.

The percentage of seminomas is slightly higher than found in most series Lewis[13] found 43 per cent seminomas

The history and examination of the patients in this series revealed the following features: The tumor was associated with a hydrocele in 5 patients One patient had a draining scrotal sinus Forty of the patients noted enlargement of the testicle. Nine patients gave a history of pain in the affected testicle. Back pain and gastro intestinal symptoms were common among the patients' first complaints A history of trauma to the testicle was elicited from five Gynecomastia was found in two Physical examination of the scrotal contents on admission of 2 patients was so nearly within normal limits that there was hesitation to

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[15] Vermooten, V and Hettler, W F The significance of gonadotropic hormones in the urine of patients with testicular tumors J Urol , 60: 519-523, 1948

[16] Dixon, Frank J and Moore, R A Tumors of the Male Sex Organs Washington, D C Armed Forces Institute of Pathology, publishers, 1952

[17] Moore, R A Teratoid tumors of testis J Urol , 65: 693-708, 1951

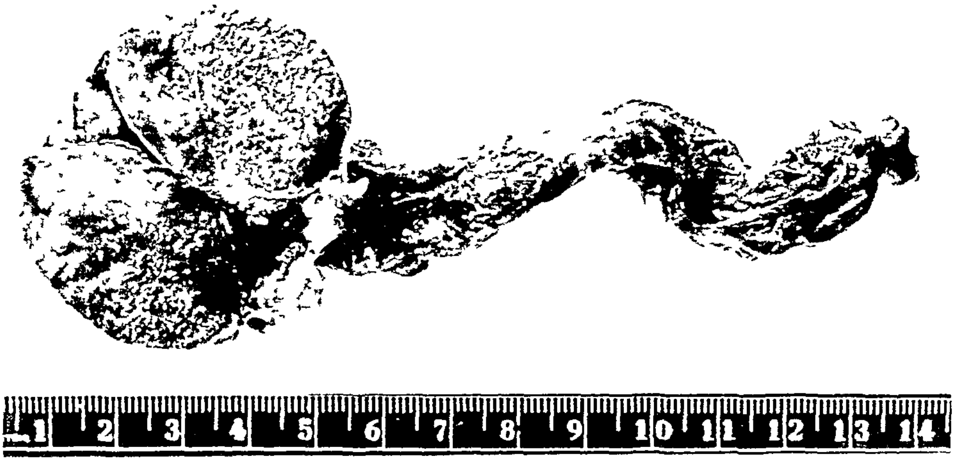

FIG. 2. First clue to testicular malignancy (teratocarcinoma) was obtained from biopsy of enlarged left supraclavicular lymph node. Note small size of original lesion.

label the testicle as pathologic (fig. 2). Confirmation was obtained only by opening the scrotum and examining the testicle directly. This should be done in any doubtful case. Hydroceles prohibit adequate examination of a testicle. They *should not be allowed to prevent or delay the diagnosis of a malignant tumor.* One patient had a hydrocelectomy 2 weeks prior to admission. The patient sought further advice when his testicle continued to enlarge. Another patient had an asymptomatic hydrocele for 7 years. Sudden enlargement and onset of pain, 4 months prior to admission, caused him to seek medical advice.

Epididymitis and orchitis have caused confusion and delay in the diagnosis of testicular cancers. One patient was admitted after having his fears allayed for 8 months by several physicians who blamed orchitis for his testicular enlargement. Another one received penicillin therapy for 6 months for epididymitis before an orchiectomy revealed the true nature of his difficulty. On the other hand, several patients failed to heed competent medical advice by delaying a proposed orchiectomy. Such advice is relatively unacceptable to the average male patient.

A tragic feature of this disease is that it can become so far advanced without the patient's being aware of his illness. Metastatic growths were found before treatment in 10 patients. Only three of the ten are still living. Metastasis was found in the peri-aortic lymphatics 8 times, chest 3 times, supraclavicular nodes 2 times and 1 time each in the skin and along the spermatic cord.

Treatment of the patient has consisted of a simple orchiectomy with amputation of the cord at the internal inguinal ring. Those who had scrotal orchiectomy elsewhere frequently had the remaining portion of the cord removed up to the internal inguinal ring. This eliminates one area which would otherwise be given x-radiation therapy.

Supervoltage therapy was given to most of these patients, using the procedure as outlined by Milton Friedman in Portman's *Clinical Therapeutic Radiology.*[18]

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[18] Portman, U V Clinical Therapeutic Radiology. New York Thomas Nelson & Sons, publishers, 1950, pp. 276–308.

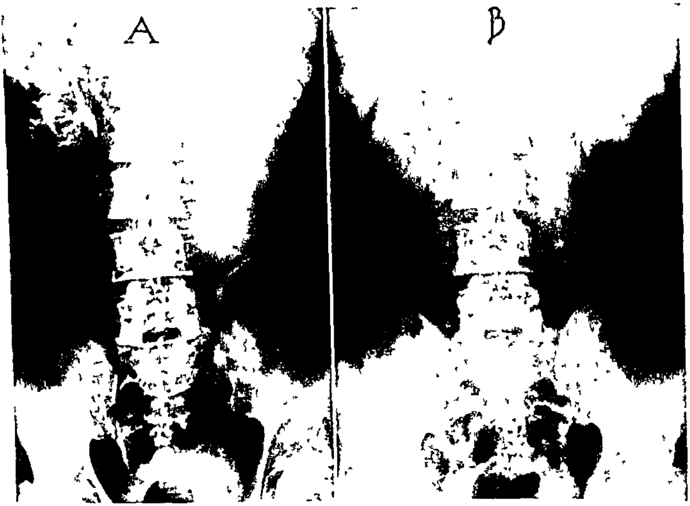

FIG 3 *A*, 2 years after left orchiectomy for seminoma. Patient not given postoperative radiation therapy Mass easily palpable. *B*, after completion of radiation therapy.

The following factors were used: 1000 kv. and HVL 3.7 mm. Pb. at 70 cm. distance. The accompanying illustrations show the locations of the ports through which therapy was given. Therapy was completed to each opposing pair of ports (anterior and posterior) before beginning irradiation to the adjacent group of ports The ideal dosage range prescribed for patients with seminoma was 2000 r in 2 weeks or its equivalent as based on time-dosage relationship. Embryonal carcinoma and teratocarcinoma received from 3000 r to 3500 r in three to four weeks. The dosage was carefully controlled in order to prevent irradiation damage to the intestines. Irradiation was given above the diaphragm only when

TABLE 2 *Seminoma*

Elapsed Time Since Therapy	Number Followed	Living Without Metastasis	Living With Metastasis	Dead
6 mos	6	3	2	1
1 yr	2	1	1	0
2 yrs	11	8	1	2
3 yrs	2	2	0	0
4 yrs	1	1	0	0
Total	22	15	4	3
	22	19		3
Per cent		86 3%		13 7%

TABLE 3. *Embryonal carcinoma*

Elapsed Time Since Therapy	Number Followed	Living Without Metastasis	Living With Metastasis	Dead
6 mo.	7	1	1	5
1 yr.	3	0	1	2
2 yrs.	0	0	0	0
3 yrs.	0	0	0	0
4 yrs.	1	1	0	0
5 yrs.	1	1	0	0
6 yrs.	3	3	0	0
Total	15	6	2	7
	15	8		7
Per cent		53.3%		46.7%

evidence of metastasis was present in the mediastinum, lungs or supraclavicular nodes.

Radical retroperitoneal lymphatic dissection was done in only 5 patients. All were given a course of irradiation. Two of these patients are dead and a third is declining rapidly. The remaining 2 patients have been well three and four years following treatment. No malignant cells were found in the lymph nodes removed from the patient who is now living 3 years postoperatively. The diagnosis was malignant teratoma in both of these survivors.

Excretory urograms were done in almost all patients as preoperative diagnostic studies in an attempt to determine the presence of early metastasis to the peri-aortic lymph nodes. It was found that lateral ureteral deviation produced by an extrinsic mass could be demonstrated even when abdominal masses could not

TABLE 4. *Teratocarcinoma*

Elapsed Time Since Therapy	Number Followed	Living Without Metastasis	Living With Metastasis	Dead
6 mo.	4	0	0	4
1 yr.	0	0	0	0
2 yrs.	1	0	1	0
3 yrs.	1	1	0	0
4 yrs.	2	2	0	0
5 yrs.	0	0	0	0
6 yrs.	0	0	0	0
7 yrs.	1	1	0	0
Total	9	4	1	4
	9	5		4
Per cent		55.5%		44.5%

TABLE 5 *Final results*

	Number	%
Total dead	15*	32%
Total living	32	68%
Total followed	47	

* One patient with an unlisted diagnosis died 1½ yrs following treatment

be felt on physical examination The deviation occurs on the same side as the diseased testicle and varies directly with the size of the metastatic mass Partial and complete ureteral obstruction with mild or severe hydronephrosis was observed Post irradiation excretory urograms were done in all patients found with ureteral deviation before therapy The rate and degree of shrinkage of the masses as shown in serial excretory urograms served as a guide to the radiosensitivity of the tumor being treated

Follow-up care, just as in primary diagnosis, was made more reliable by the use of the excretory urograms in determining the presence of early lymphatic spread Our follow-up examinations consisted of an interval history, physical examination, chest x-ray and excretory urograms It is felt that such studies at approximately 6-month intervals will insure the patient the best possible care Careful observation of the remaining testicle should always be a part of the follow-up care

There was a follow-up of 47 of the 50 patients (table 5) Thirty-two, or 68 0 per cent, are alive Tables 2, 3 and 4 show the number and percentage who have survived with each of the three types of tumors The highest survival rate was in the seminoma group, 86 3 per cent of 22 cases Fifty-three per cent of 15 patients with embryonal carcinoma are alive while 55 per cent of 9 patients with teratocarcinoma have survived

All of the deaths from embryonal carcinoma and teratocarcinoma occurred within one year after treatment Those who survived the first year are apparently cured While only 3 patients from the seminoma group are dead, two of these lived for two years after treatment This reveals the rapidity of the course of the disease in embryonal carcinoma and teratocarcinoma and the somewhat less rapid course of seminoma

SUMMARY

An analysis of the clinical features, pathology and follow-up data on 50 cases of malignant testicular tumors has been presented Sixty-eight per cent of the 47 patients followed are alive Eighty-six per cent of the seminoma group, 53 per cent of the embryonal carcinoma group and 55 per cent of the teratocarcinoma group are alive

Properly administered supervoltage x-ray therapy is emphasized and the results of such therapy are given

The use of the excretory urogram is emphasized in revealing early metastasis to the periaortic lymph nodes Serial studies of this type are of value in determining the radiosensitivity of peri-aortic masses since changes will be found in the curvature of the ureter or relief of its obstruction as the metastatic deposit shrinks in size.

A routine of follow-up care is outlined.

A case of concomitant bilateral embryonal carcinoma of the testicles is reported bringing the total bilateral concomitant testicular tumors in the literature to thirty. A case of bilateral seminoma of the testicles in a bilateral cryptorchid pseudohermaphrodite is reported bringing the recorded total to nine.

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RETROPUBIC PROSTATECTOMY: A MODIFICATION OF TECHNIQUE USING A COMBINED PROSTATOVESICAL INCISION

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The retropubic approach to the prostate, as revived by Millin, has now become one of the acceptable procedures for the relief of prostatic obstruction. The effectiveness of this operative method has now been established and its usage is becoming more popular with the urological profession. It is particularly indicated for hyperplasias of large size and is especially adaptable to glands which lie high in the pelvis in nonobese individuals where excellent exposure is easily obtained beneath the symphysis pubis. With the use of antibiotics prevesical infections and other disturbing complications such as osteitis pubis have curiously decreased over the past 5 years. The major advantages claimed for this approach, as described by Millin, have been an early and oftentimes primary closure of the incision into the urinary tract without urinary drainage, as well as the singular lack of postoperative vesical irritability. In cases in which good exposure is possible, fulguration or ligation of the bleeding vessels within the prostatic capsule aids in the control of hemorrhage. This exposure through the prostatic capsule avoids an incision in the bladder, as is done in the customary suprapubic prostatectomy. Opening the bladder accounts for the postoperative vesical irritability and the often frequent establishment of a suprapubic urinary fistula which heals by secondary intention.

Most urologists have followed the technique of Millin which consists of a transverse incision in the anterior prostatic capsule at a point about midway between the bladder and the prostatic apex. However, Millin's transverse prostatotomy often leaves much to be desired in providing room for the operator's finger to enucleate a particularly large adenoma. For enucleation of large adenomas a very wide transverse capsulotomy is necessary for deliverance of one large lobe at a time but even then lateral capsular tears may occur resulting in division of the lateral arteries leading to active bleeding. Such tears may also prevent adequate water-tight closure following the enucleation. In addition, the use of the routine transverse incision or prostatotomy fails to allow adequate inspection and appraisal of the vesical neck where contractures and small median hypertrophies may exist. In order to visualize the vesical orifice, tenacula must be applied to the superior margin of the prostatotomy incision for retraction. This may distort and give a false sense of security concerning the adequacy of the vesical outlet before closure, resulting in inadequate wedge resections of the vesical neck. Furthermore, it does not always result in good exposure of the prostatic fossa after removal of the adenoma so that the placement of hemostatic sutures in the vesical neck for active bleeding through such an incision may be difficult.

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Operators at times have varied Millin's transverse prostatotomy and used a simple vertical midline incision which has the advantage of avoiding division of the arborizing venus plexus of Santorini over the capsule and of the prostatic arteries which sometimes project rather far around the lateral aspects of the prostate. On the other hand, the usual vertical capsulotomy which is confined to the prostatic capsule is often far too short to adequately remove the adenoma when the latter is of large size and thus has the disadvantages mentioned above in relation to the transverse capsulotomy. Extension of the capsular incision far down into the apex to gain room may possibly damage the external sphincter leading to incontinence. Suture of the opening in the prostatic capsule in a water-tight manner in which primary healing is likely may be difficult because of the inaccessibility of the distal end of the incision deep down behind the symphysis pubis.

It is the purpose of this communication to describe the author's experiences with a variation in technique which avoids the transverse incision into the prostatic capsule. The prostatotomy which we are herewith reporting is designed to eliminate many of the undesirable features of both the Millin transverse and the customary vertical incisions into the prostatic capsule. We use instead a modified vertical incision extending from the midprostatic region upward through and *including the vesical neck* which is avoided when the customary vertical incision is restricted to the prostatic capsule below the bladder. This incision allows a more adequate exposure for enucleation of the adenoma and management of the vesical neck and hemostasis.

OPERATIVE TECHNIQUE

As illustrated (fig. 1), a transverse abdominal skin incision of the Pfannenstiel type is employed. The anterior surface of the bladder just above the prostate and the prostatovesical junction are exposed by blunt dissection. Reflection of the peritoneum from the anterior surface of the bladder is necessary only for a short distance as the incision into the bladder does not extend very high. The peritoneal reflection is held backward by a self-retaining retractor or spatula of the Harris-Vest type. Care is taken to eliminate any development of the lateral fossa (necessary when a Millin transverse capsulotomy is used) which usually leads to bleeding from the periprostatic venous and sometimes arterial plexuses. The operator's left hand, appropriately gloved, is inserted into the rectum for counterpressure on the prostate. Elevation of the gland expedites the subsequent prostatotomy and enucleation. A vertical incision is then made through the prostatic capsule beginning about midway between the apex and at the base of the gland on its anterior surface. Slight deviation from the midline may be necessary to elude large vessels but this in no way affects the ultimate procedure. The incision is extended upward to include the (anterior) vesical orifice. A plane of cleavage is developed between the adenoma and the false capsule following which the apex of the urethra is divided with the index finger of the operating hand pressed against the index finger of the opposing hand within the rectal cavity. If the urethra does not easily break at the apex, it is best to divide the mucosa with

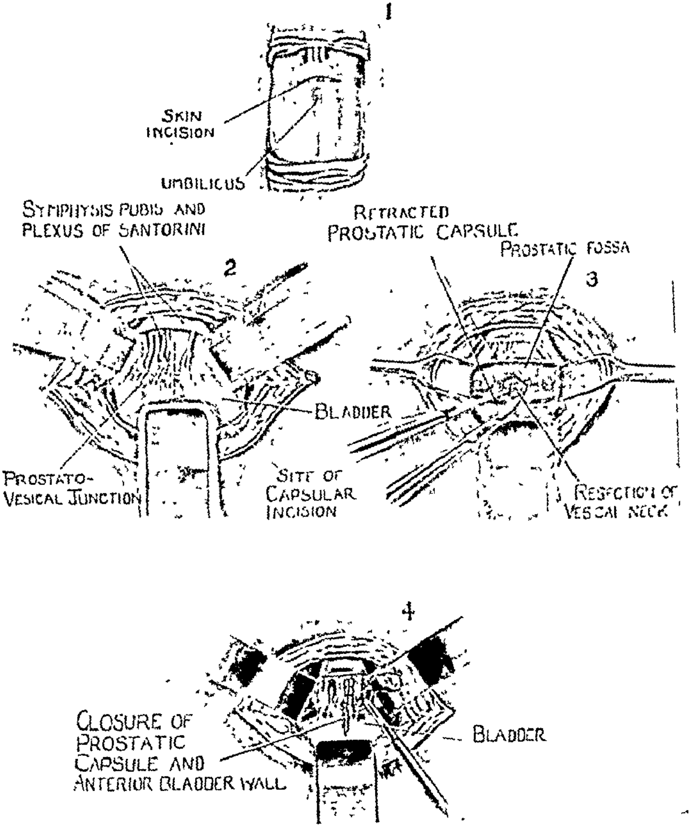
1
SKIN INCISION
UMBILICUS
SYMPHYSIS PUBIS AND PLEXUS OF SANTORINI
2
BLADDER
PROSTATO-VESICAL JUNCTION
SITE OF CAPSULAR INCISION
RETRACTED PROSTATIC CAPSULE
PROSTATIC FOSSA
3
RESECTION OF VESICAL NECK
4
CLOSURE OF PROSTATIC CAPSULE AND ANTERIOR BLADDER WALL
BLADDER

Fig 1 *1*, Transverse incision through skin and fascia with recti muscles retracted laterally *2*, Anterior surface of prostate and lower portion of bladder exposed Dotted line indicates site of "combined incision" to include vesical neck *3*, Note excellent exposure of prostatic fossa and excision of vesical neck after removal of adenoma *4*, Continuous catgut suture is used to close vertical incision in prostatic capsule and divided vesical orifice tightly

scissors to prevent avulsion of the urethral membrane down into the prostatomembranous area and possibly damage the external sphincter mechanism. Enucleation of both or each lobe separately is then easily performed.

This exposure allows a careful debridement of the prostatic fossa and excision of the posterior vesical neck, when warranted, under vision. Small retractors of the Deaver type inserted into the prostatic capsule allow the posterior vesical lip to be visualized as well as the floor of the prostatic fossa where intracapsular bleeding can be controlled by electrocoagulation. Sutures can be placed to obliterate any large vessels when present. Following satisfactory control of the bleeding a 24F, 30 cc Foley hemostatic bag catheter is inserted into the bladder and inflated.

The prostatotomy is then closed with either interrupted or continuous sutures to insure a water-tight closure. Closure of the vertical incision is technically easier than suturing the transverse capsulotomy. The retropubic space is drained by a simple Penrose drain and the abdominal wound closed in the usual fashion with interrupted chromic sutures so that the patient can become ambulatory on the second postoperative day. The Foley bag is ordinarily allowed to remain in the bladder and is not pulled into the prostatic fossa. It is our belief that venous ooze in the prostatic fossa is more likely to promptly cease if the prostatic capsule is allowed to collapse rather than prolong its dilatation by the presence of an inflated hemostatic bag catheter. Intermittent irrigation of the catheter is carried out just as following transurethral resection until complete hemostasis is obtained, following which the Foley bag is deflated to about 5 or 10 cc. This decreases the size of the foreign body in the bladder and leads to less vesical irritability.

In most instances the prostatovesical incision is healed by the fourth to sixth postoperative day when the catheter can be removed for the resumption of normal micturition. The suprapubic Penrose drain is shortened daily and is usually out by the third postoperative day unless excessive wound seepage warrants its retention. In a rare case in which the wound is not healed, as evidenced by urinary drainage, the catheter is simply re-inserted for several days. Some form of antibiotic therapy is usually instituted for the three or four postoperative days.

A survey has been undertaken to evaluate the results obtained employing this combined prostatovesical incision with a similar number of consecutive suprapubic prostatectomies using postoperative hospital stay and postoperative catheter life as a basis for comparison. Thirty-three patients (both private and ward) have been operated on in whom the described technique was used (see table 1). It will be noted that the average postoperative hospitalization and

TABLE 1

Operation	Cases	Average P. O. Catheter Life	Average P.O. Hospitalization	Morbidity	Mortality
Retropubic prostatectomy (combined prostatovesical incision)	33*	7.2 days Range: 5–22 days	8.9 days Range: 7–23 days	Temporary suprapubic drainage—1 case (catheter replaced)	1 case (pulmonary embolus 10th p.o. day)
Classical suprapubic prostatectomy with suprapubic drainage	33*	16.3 days Range: 5–39 days	19.0 days Range: 7–41 days	Delayed closure of suprapubic fistula —16 cases	None

* Consecutive cases.

catheter life required following the suprapubic procedure were more than double that encountered in those patients treated by retropubic prostatectomy with this modification in technique It has, therefore, been concluded that extension of the capsular incision into the vesical neck and anterior bladder wall in order to provide better exposure *does not* result in delayed wound healing or the development of suprapubic fistulas

COMMENT

It should be noted (fig 1) that 65 to 70 per cent of the total length of this modified incision is through the prostatic capsule with the remaining portion just into the bladder including the vesical neck It is particularly adapted for enucleation of any median or subtrigonal lobes and proper resection of the posterior vesical neck which is usually necessary in retropubic prostatectomy in order that late contractures and obstructions will not develop Adequate excision of the posterior vesical neck is mandatory with this technique because of the division of the anterior vesical neck but we have found this desirable rather than disadvantageous The use of this type of incision provides such adequate exposure that fulguration of bleeding points within the prostatic fossa under direct vision, proper treatment of (posterior) vesical neck abnormalities and, if necessary, the placement of ligatures for hemostasis in the posterior quadrants of the vesical neck are greatly facilitated With adequate control of hemorrhage thus possible *in most cases, there is seldom need for a suprapubic catheter and in all instan* we have been able to close this prostatovesical incision tightly by continuou or interrupted sutures of catgut so that it is followed by a high percentage o primary closures It is true that long incisions into the bladder in which the do is approached also can be tightly closed by approximating sutures with suprapubic catheter drainage but the leakage of urine postoperatively is uncommon leading to delayed healing The short incision into the an surface of the bladder to include the vesical neck is not followed by the bla irritability frequently encountered following suprapubic prostatectomy in case a long incision into the bladder is necessary for insertion of the hand least several fingers The technique herein described is just as simpl customary suprapubic prostatectomy with the added advantage that enu of the adenoma through a divided vesical neck is easier than other t of retropubic prostatectomy

CONCLUSIONS

A variation in the technique of prostatotomy for retropubic prostat been reported from experience in 33 cases This operative procedure limited vertical incision in the prostatic capsule which avoids the arterial supply on the lateral surface of the prostate so that it is with minimal bleeding

The incision includes the vesical neck which allows more ad than possible with the transverse prostatotomy popularized by

The better exposure expedites excision of the posterior vesi trigonal enlargements and allows better control of hemorrhage

At the same time it involves only a small incision in the lower (thick) segment of the bladder which avoids the occasional disadvantages of suprapubic prostatectomy, i.e., vesical irritability, inadequate control of hemorrhage and the frequent necessity of suprapubic drainage and healing by secondary intention with a urinary fistula.

In our experience 32 out of 33 cases healed per primam without suprapubic urinary drainage accompanied by minimal vesical irritability.

The average postoperative hospitalization is less than 9 days.

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SPONTANEOUS AFIBRINOGENEMIA IN CANCER OF PROSTATE: REPORT OF TWO CASES

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Afibrinogenemia is, by definition, the absence in the blood of fibrinogen, the soluble protein in the plasma which is converted by the action of thrombin into fibrin, thus producing coagulation of the blood. Several cases of spontaneous afibrinogenemia have been reported, resulting from abnormal activation of a trypsin like enzyme called fibrinolysin, which normally exists in the blood only in an inactive form. When activation is brought about by some unknown cause the active enzyme dissolves fibrin clots and also digests fibrinogen and other plasma proteins. Tagnon reported 2 patients with cancer of the prostate with extensive metastases who showed a bleeding tendency associated with fibrinolysis, but he did not demonstrate afibrinogenemia. In 1943 Huggins and associates found fibrinolytic and fibrinogenolytic enzymes in prostatic fluid, and it has been suggested that the prostatic cancer cells may have been the source of the enzyme responsible for the fibrinolysis in Tagnon's cases. The prostatic cancer cells may have produced sufficient prostatic fibrinolysin to have caused the fibrinolysis and the resulting hemorrhagic diathesis.

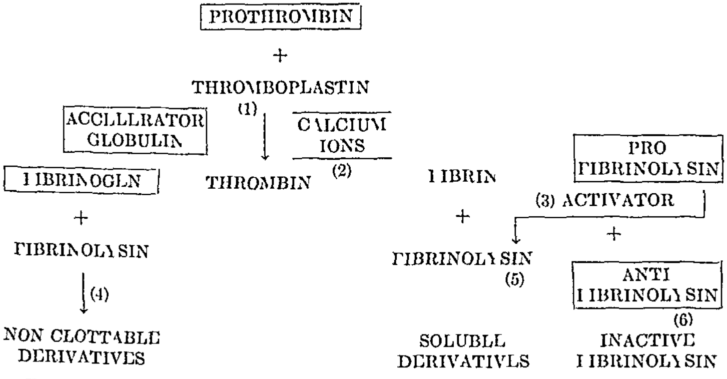

Fig. 1. Simplified diagram of blood clotting and fibrinolytic action. Factors inclosed in rectangles exist normally in blood.

Reactions 1 and 2 represent normal clotting which results from thromboplastin production at a wound or other foreign surface.

Reaction 3 is brought about by various tissue activators, most of which are not well characterized. Hemolytic streptococci produce an activator called streptokinase.

Active fibrinolysin efficiently digests both fibrinogen and fibrin clots: reactions (4) and (5). If sufficient fibrinolytic activity is present, complete afibrinogenemia will result; moderate activity results in low fibrinogen levels.

Antifibrinolysin provides partial protection against fibrinolysin activity, reaction 6.

Read at annual meeting, Western Section of American Urological Association, Victoria, B. C., April 19–22, 1954.

CASE REPORTS

Case 1. Mr. C. H. L., No. 13520333, aged 43, was admitted to the Los Angeles County General Hospital with back pain of 21 months' duration and with progressive urgency, frequency, and hematuria for the past 2 months. Early in his illness a transurethral resection of the prostate had been done elsewhere and the histological diagnosis of adenocarcinoma of the prostate established. On 10 mg. of stilbestrol daily he had been able to return to work for a time, but had given it up because of the progressive severe back pain. The past and family histories were otherwise entirely negative.

Physical examination revealed a well developed and nourished white man of the stated age, and in no apparent distress. Blood pressure was 118/70, temperature 99.2, and pulse 80. The only abnormal physical findings were moderate gynecomastia, atrophic testes, and a small, hard and fixed prostate gland. Hemoglobin was 13.5 gm. and the white cell count was 10,000. The urine was grossly bloody. The nonprotein nitrogen was 25 and the serum acid phosphatase was 1.6 units (normal 1 to 4 units).

Three days after admission a bilateral orchiectomy was performed. There was no unusual bleeding. Four days later transurethral resection of the prostate was done under spinal anesthesia. The patient was nauseated and restless during the operation and there was moderate, but not excessive, bleeding. One transfusion of 500 cc of whole blood was given on the table and the blood pressure was never less than 105/60. Irrigation of the bladder after the procedure was slightly more bloody than usual, but was considered satisfactory. The operation was completed in 45 minutes, and the patient was returned to bed with tension on the Foley catheter. He did complain of feeling chilly.

About an hour and a half after his return to the ward the drainage became very bloody and an additional 500 cc of whole blood was started. Three hours after the end of the operation he was in shock, the blood pressure was 60/50, pulse 128, and hemoglobin down to 11 gm. A blood specimen taken for typing and crossmatching was reported as not clotting, and furthermore that the blood specimen of the day before, taken for typing, was unclotted.

Seven hours after surgery, with blood or plasma having been continuously administered, tests by the chief chemist of the hospital indicated that bleeding was due to a lack of fibrinogen. When the patient's blood was mixed with normal blood there was no clot delaying effect, which indicated that it did not contain heparin or other anticoagulants. The addition of potent thrombin to the patient's blood produced no clotting. Seven and one-half hours after surgery there was some evidence of clot formation in the patient's blood, but it was a very poor clot. Quantitative determinations of the fibrinogen level of the plasma showed no detectable fibrinogen until one specimen taken 9 hours and 10 minutes after surgery showed a level of 16 mg. per 100 cc (normal 250 to 300 mg.). Specimens taken 16 hours and 24 hours after the operation showed 78 and 104 mg., respectively. On the third day the level was 310, and at 11 days it was 290.

At the end of 22 hours the blood pressure had varied from 60/40 to 100/60 and the hemoglobin was 10.5 gm. despite the administration of 6000 cc of whole blood and 1250 cc of plasma, of which 250 cc was fresh antihemophilic plasma. By this time the blood seemed to clot satisfactorily, but the bleeding continued and the situation was complicated by the poor drainage incident to the bladder filling with clots. A suprapubic cystostomy was therefore done 24 hours after the first operation and the fossa packed with 30 pieces of oxycel gauze. Four additional pints of blood were given that day, the bleeding was finally controlled, and the patient was out of shock with a blood pressure of 110/65.

Two days following operation the patient was oliguric and this developed into lower nephron nephrosis, with all its problems. The nonprotein nitrogen went up to 340 on the sixteenth postoperative day. During this oliguric phase the most marked hypocalcemia was on the ninth day, when the level of calcium was 3.0 mEq/L. On the same day the potassium level was 8.56 mEq/L. During the diuretic stage the most marked hypopotassemia was on twenty-fourth day, when serum potassium was 2.9 mEq/L. The nonprotein nitrogen gradually came down to 28 on the thirtieth day, the day before death. Fluid and electrolytes were given throughout the course as indicated by the laboratory determinations daily, and the foregoing figures represent the maximum deviations from the normal.

Many other problems were encountered such as nausea, vomiting, diarrhea, severe stomatitis, drug reactions, difficult parenteral feedings, and others. Falling blood pressure at times required 50 mg. of neosynephrine in 500 cc of 5 per cent glucose by intravenous drip over an 8-hour period to maintain a systolic pressure of 80. The patient's final undoing was uncontrollable infection. On the twenty-second postoperative day a blood culture was positive for Staphylococcus aureus, coagulase positive, and resistant to penicillin, streptomycin, aureomycin, and terramycin. It was only moderately sensitive to chloromycetin and bacitracin. Chloromycetin was not available for parenteral use, but bacitracin was given both intravenously and intramuscularly to no avail. The patient had jaundice and temperature ranges from 104 to 106 during his last 4 days, and he expired on the thirty-first postoperative day.

Necropsy revealed multiple lung abscesses from 0.5 to 1 cm. in diameter and multiple abscesses in both kidneys. Cultures from these abscesses showed the same Staphylococcus aureus, coagulase positive, and a mixture of gram-negative coliform bacilli. There was an incidental finding of multiple polyposis of the colon, with malignant degeneration.

Case 2. Mr. W. H., No. 973029, aged 76, was first admitted to the Los Angeles County General Hospital on May 23, 1946, complaining of bilateral inguinal adenopathy for 6 months, associated with pain and edema of the left leg for 10 days. Biopsy of an inguinal gland at another hospital had shown metastatic carcinoma, and rectal examination revealed a hard, fixed, irregular prostate, grade 3, consistent with prostatic carcinoma. The nonprotein nitrogen was 39 and the serum acid phosphatase 8.2 units. X-rays of the urinary tract revealed metastatic osteogenic neoplasm of the fourth lumbar vertebra and in the right sacro-iliac area. The patient refused orchiectomy and was started on stilbestrol. He did, however, undergo orchiectomy elsewhere the same year, and in 1950 had a transurethral resection, with positive biopsy. This also was done elsewhere.

He was re-admitted in May 1951, because of back and leg pains, at which time the nonprotein nitrogen was 34 and the serum acid phosphatase was 9.8 units. Chest x-rays showed extensive metastases and the lumbar and pelvic bones exhibited advanced osteoblastic metastases. He returned on February 11, 1953 because the pains were uncontrollable. The nonprotein nitrogen then was 98 and the serum acid phosphatase was 11.6 units. He was started on TACE which seemed to relieve the pain until April of the same year, when it returned but with less severity. On October 31, 1953, he came back with the same complaint of pains scattered throughout the pelvis and back. Nonprotein nitrogen was 33, serum acid phosphatase 7.8 units, and hemoglobin 8.5 gm. Stilbestrol was substituted for TACE and he was discharged.

The last admission, on March 19, 1954, was occasioned by grossly bloody urine for 2 days. This was associated with multiple purpuric spots, up to 5 cm. in diameter, on the arms and trunk. One small abrasion on the wrist kept oozing in spite of pressure bandage. The hemoglobin was down to 7.5 gm. A tentative diagnosis of fibrinolysis and afibrinogenemia was made and blood was drawn for clotting time, fibrinogen determination, typing, and cross-matching. The clot formed slowly and poorly, and in a water bath at 37 degrees C. it was lysed completely in less than five hours. The fibrinogen determination was 65 mg. per cent, about 21 per cent of the normal 250 to 300 figure. At 5 p.m. on the day of admission a transfusion of whole blood was given. With the diagnosis of fibrinolysis established, the patient was also given desiccated anti-trypsin* intravenously on two occasions in conjunction with transfusions. Since trypsin and fibrinolysin are very similar enzymes it was suggested that the antitrypsin enzyme might be valuable in preventing the lysis of the fibrin, inasmuch as pure fibrinogen was not available. After the antitrypsin blood transfusions three specimens of blood were tested for fibrinolysis and none showed it after 48 hours. Quantitative fibrinogen levels were recorded as follows:

March 19	5 p. m.	65 mg. per cent
March 20	3:30 a. m.	138 mg. per cent
March 20	8:05 a. m.	190 mg. per cent
March 20	12:45 p. m.	206 mg. per cent
March 20	7:00 p. m.	155 mg. per cent

The following day the hematuria had decreased and by the morning of the third day had completely disappeared. The purpuric spots showed distinct regression by the third day. A total of four transfusions were given and the hemoglobin was brought up to 12 gm.

COMMENT

In contrast to the cases reported by Tagnon, afibrinogenemia was proven in our first case, but fibrinolysis was not. In the second patient both afibrinogenemia and fibrinolysis were demonstrated. It is entirely possible that the blood examined the day before surgery in our first patient may have formed a clot, but that the clot may have been lysed by the time it was checked the next afternoon It is customary in the hospital to type and cross-match the blood the afternoon before surgery and the laboratory ordinarily reports any abnormality and refuses to supply the blood for transfusion Since there was no protest in this case and the blood was set up it seems fair to assume that the specimen from the patient appeared normal at that time, this is only an assumption, and cannot be accepted as a fact By the time we had established the diagnosis of afibrinogenemia the patient had received so many transfusions that the proof of fibrinolysis could not be established

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* Soy bean trypsin inhibitor was furnished through the courtesy of Mr. Eugene C. Loomis of Parke, Davis, and Company.

The exact mechanisms of the enzyme systems in such cases need more work both from the research and clinical aspects before they can be clearly understood Lysis of the fibrin so important in wound healing may be a factor in at least some instances of wound dehiscence, but here too more research study is necessary

SUMMARY

Proven afibrinogenemia as a cause of severe hemorrhage in 2 patients suffering with cancer of the prostate is reported, one following transurethral resection and the other associated with extensive metastases

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FURTHER STUDIES IN DETECTION AND DIAGNOSIS OF PROSTATIC CARCINOMA

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Since the pioneering experiments of Gutman and Gutman,[1] it has been generally accepted that constant elevations of the total acid phosphatase of blood serum are produced only by prostatic metastases or extensions. Marshall[2] warns us, however, that this test requires an expert technician and experience in interpreting the findings. The utility of the test has been further restricted because normal values have been found in large percentages of cases with widespread metastases[3] and elevated values only in small percentages of patients with early prostatic carcinoma.[4]

In spite of the faults inherent in the method, however, there was indication of a close relationship between elevated serum acid phosphatase levels and prostatic carcinoma, a relationship that is not paralleled by other commonly occurring malignancies. Such a relationship should have given early impetus to attempts to improve and perfect the method by those groups interested in diagnostic tests for malignancy.

Abul-Fadl and King observed in 1948[5] that tartrate completely inhibited acid phosphatase extracted directly from surgical specimens of human prostates. They further reported that acid phosphatase derived from erythrocytes was not inhibited. Abul-Fadl and King did not apply this observation and there were no published reports of its application until 1953 when the brilliant investigations of Fishman and Lerner[6] appeared. These latter named authors reported that measurement of the tartrate inhibited acid phosphatase of serum was a more sensitive indicator of the amount of acid phosphatase derived from the prostate than total acid phosphatase. They presented evidence to support the viewpoint that in male subjects the greatest portion of tartrate inhibited serum acid phosphatase is most likely of prostatic origin.

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Others had utilized [illegible] hyde to eliminate acid phosphatase derived [illegible] dehyde to inactivate erythrocyte acid phosphatase followed by alcohol to partially inactivate the remaining prostatic acid phosphatase[9] [10] None of these authors presented convincing statistical evidence that their methods would meet the requirements of a diagnostic test for malignancy as set forth by Dunn and Greenhouse[11]

We attempted to repeat the experiments of Fishman and Lerner[6] and found their method quite inconvenient and fraught with errors, both inherent and manipulative Although we were eventually able by painstaking endeavor to duplicate their results and to confirm the essential principles of their method, we found it unsuitable for routine and rapid examination of large numbers of samples After a very extensive period of study, trial and futile attempts at simplification, we abandoned use of their method.

We have developed, however, a simple, practical method of the determination of serum acid phosphatase of prostatic origin The principle is based on the tartrate inhibition of acid phosphatase demonstrated by Abul-Fadl and King and first applied by Fishman and Lerner Nitrophenyl-phosphate,* [12] however, is utilized as the substrate in contrast to phenyl-phosphate which was used by the aforementioned workers Details of the method will be published elsewhere

The purpose of this communication is to present statistical evidence of the utility of our newly developed method for the determination of serum prostatic acid phosphatase Over 4000 subjects have been studied to date The present report deals with a total of 1106 subjects whose clinical evaluation is now complete

CLINICAL MATERIAL SOURCES

Blood samples were collected from patients in the wards and clinics of the following hospitals.

Jefferson Hillman Hospital, Birmingham, Ala
Veterans Hospital, Birmingham, Ala
St Vincent's Hospital, Birmingham, Ala
West End Baptist Hospital, Birmingham, Ala
Carraway Methodist Hospital, Birmingham, Ala
Lloyd Noland Hospital, Fairfield, Ala

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U. S. Marine Hospital, Mobile, Ala.
Blessed Martin de Porres Hospital, Mobile, Ala.
Jackson Memorial Hospital, Miami, Fla.
Dade County Hospital, Miami, Fla.
Mt. Sinai Hospital, Miami, Fla.
Mercy Hospital, Miami, Fla.

Samples were also collected from patients attended by physicians in private practice in the Birmingham, Mobile and Miami areas. Through a co-operative program with the Cancer Institute at Miami, blood samples were made available from patients upon whom prostatic cytology studies had been performed. Histological data on all the Alabama cancer bearing subjects were secured through clinical records and checked with the Tumor Registry of the Alabama Association of Pathology.

Grateful acknowledgment is deserved by all of the medical personnel and the institutions and hospitals that co-operated with us to make possible the rapid performance of this research project.

CLASSIFICATION OF SUBJECTS

1) Criteria of normal group. The 185 subjects included in this category were normal males with no clinical evidence of disease. In a great many cases the subjects were given a complete physical by their physicians with the finding of no evidence of disease. A few subjects were blood donors with normal serology and hematology and no evidence of fever. A large number of subjects were from an industrial population of males above the age of 45 with no evidence of disease revealed by blood pressure measurements, electrocardiograms, blood sugar determinations, serology. In all of these subgroups the age of the normal males was heavily weighed to include an adequate number in the age group where prostatic carcinoma occurs.

2) Criteria of nonmalignant disease group. The 655 subjects included in this category were well documented, well studied male patients with a variety of disorders other than carcinoma. Included in this group were a great preponderance of patients with benign prostatic hypertrophy, prostatitis and other pertinent nonmalignant urological disorders. It was, of course, impossible to secure prostatic tissue for histological studies of this entire group but whenever possible prostatic histologic data were secured. Prostatic cytology was performed on some members of this group but not on all.

3) Criteria of cancer other than prostatic carcinoma group. The 158 subjects in this group were all well documented, well studied cases of carcinoma, sarcoma and leukemia. The carcinoma cases were, for the most part, histologically confirmed and the leukemia cases by hematological and bone marrow studies. Inclusion of 78 women in this group, while furnishing valuable information as to extraprostatic sources of tartrate inhibited acid phosphatase, is obviously of no clinical importance in the diagnosis of carcinoma of the prostate.

4) Benign prostatic hypertrophy group. The 236 subjects included in this group were, for the most part, elderly males with clinical benign prostatic hypertrophy not requiring surgical procedures and hence not confirmed histologically. Wherever tissue was surgically removed, histological confirmation was sought. It is to be remembered, however, that such histological data *cannot* thoroughly rule out prostatic carcinoma since most surgical procedures for benign prostatic hypertrophy involve only the removal of the adenomatous portion of the gland. Prostatic cytology was performed on some of the subjects in this group.

5) Prostatitis group. The 78 subjects in this group included some young males with acute Neisserian infections but consisted principally of elderly males with chronic prostatitis. A good portion of the elderly male group also showed clinical evidence of benign prostatic hypertrophy. It is again obvious that adequate histological studies were not possible on the entire group studied. Cytological studies were performed on a small portion of the subjects in this group.

6) Criteria of malignancy of the prostate. 108 patients were judged to possess prostatic carcinoma if compelling clinical signs and/or histological and cytological evidence were available. Radiological evidence of bone metastasis was available in a great many cases. Cases where cytodiagnosis was positive without confirmatory histological evidence or compelling clinical or radiological signs are not included in this series.

COLLECTION OF SAMPLES FOR ANALYSIS

Blood samples were taken by venipuncture in the antecubital space of the arm, preferably before rectal or genito-urinary examination or prostatic massage had been performed. If these procedures had been undertaken, at least 24 hours was allowed to elapse before the blood sample was taken. The blood was collected in plastic tubes provided with paraffined corks. The samples were allowed to stand at room temperature only until they clotted but in any case no longer than one-half hour. They were then refrigerated and within a few hours were centrifuged in the refrigerated centrifuge to obtain the cell free serum. Aliquot portions of 1 cc were placed in plastic tubes and the samples analyzed immediately or tightly stoppered and stored in the frozen state at −20°C until analyzed. Serum from the Mobile, Alabama and Miami, Florida areas was shipped by air express in stainless steel thermos jugs packed with solid carbon dioxide. In case the whole serum sample was frozen, it was thawed at a low temperature and thoroughly mixed by stirring before an aliquot was taken for analysis. Samples which showed gross hemolysis were discarded and duplicate samples secured whenever possible.

RESULTS

Frequency distribution curves of the groups of subjects studied are presented in bargraph form in fig. 1 *A*, *B*, *C* and *D* and fig. 2 *A* and *B*. Temporarily, and somewhat arbitrarily, we have chosen the value of 0.7 units as the critical point. Above this value 100 per cent of the untreated cases of carcinoma of the prostate occurred.

A summary of the proportions positive, that is, above 0.7 units in each group is as follows:

	per cent
1. Normal	0
2. Nonmalignant disease	10
3. Nonprostatic cancer	
Male	4
Female	8
4. Benign prostatic hypertrophy	5
5. Prostatitis	8
6. *Prostatic* cancer (untreated)	100

In the normal group (fig. 1, *A*), no values above 0.65 units were noted.

In the nonmalignant disease group (fig. 1, *B*), 10 per cent of the subjects showed values above 0.7 units, but no values in excess of 1.3 units. In general it was observed that after the acute phases of the nonmalignant disease had sub-

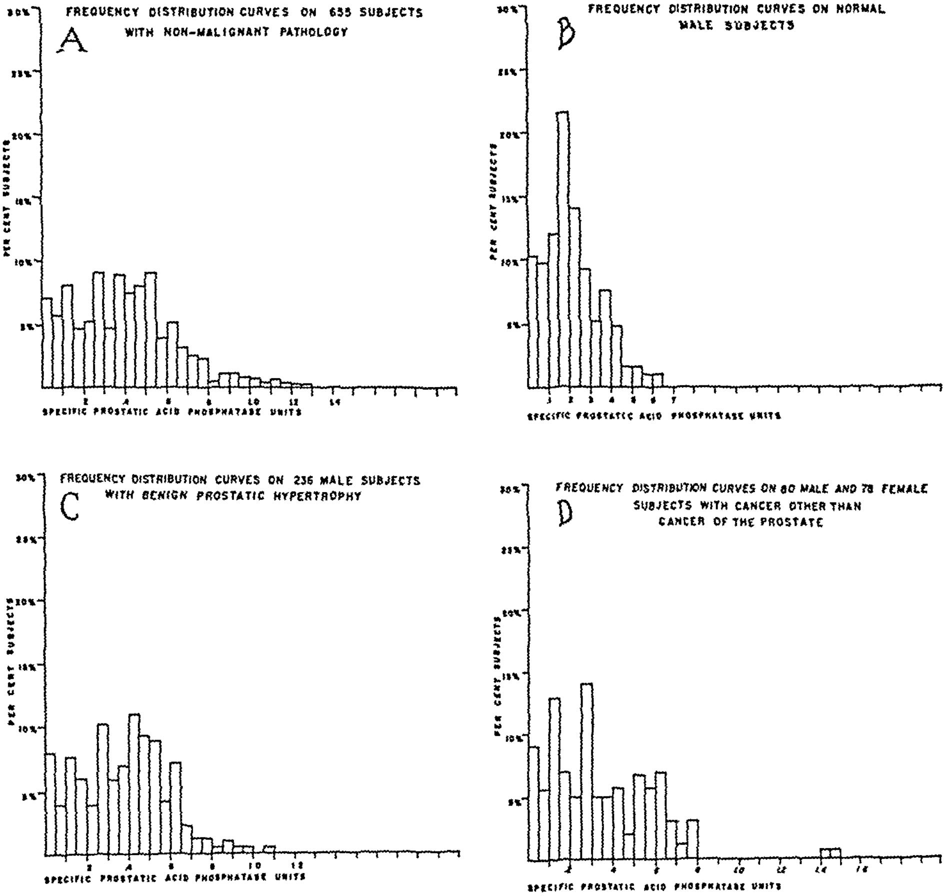

FIG. 1. *A*, frequency distribution curves on 185 normal male subjects Specific prostatic acid phosphatase units versus per cent subjects. *B*, frequency distribution curves on 655 subjects with nonmalignant disease. Specific prostatic acid phosphatase units versus per cent subjects. *C*, frequency distribution curves on 80 male and 78 female subjects with cancer other than in prostate. Specific prostatic acid phosphatase units versus per cent subjects. *D*, frequency distribution curves on 236 male subjects with benign prostatic hypertrophy. Specific prostatic acid phosphatase units versus per cent subjects.

sided, either spontaneously or due to therapy, the values decreased to below 0.7 units. These disorders include hepatitis, cirrhosis, liver damage, constipation and diarrhea, gallbladder disease, hydrocele, functional gastric disorders, inguinal hernia, asthma, hemorrhoids, dermatitis of the penis, sciatica, irritable colon, diabetes, cone bladder, miliaria rubra, urethral hemorrhage, fibrositis, kidney stones, chronic pyelonephritis with uremia, gastro-enteritis, intestinal obstruction, prostatitis and benign prostatic hypertrophy. Prostatic massage and disorders eliciting spasm in areas near the prostate must be suspect in interpreting values between 0.7 and 1.3 units. We have no evidence as yet that physiological spasm might be responsible for elevations above 0.7 units.

None of the nonprostatic cancer group (fig. 1, *C*) showed elevations above 1.5 units and only 4 per cent of the total were falsely positive. These false positive cases were easily diagnosed cases of leukemia, carcinoma of the head of the

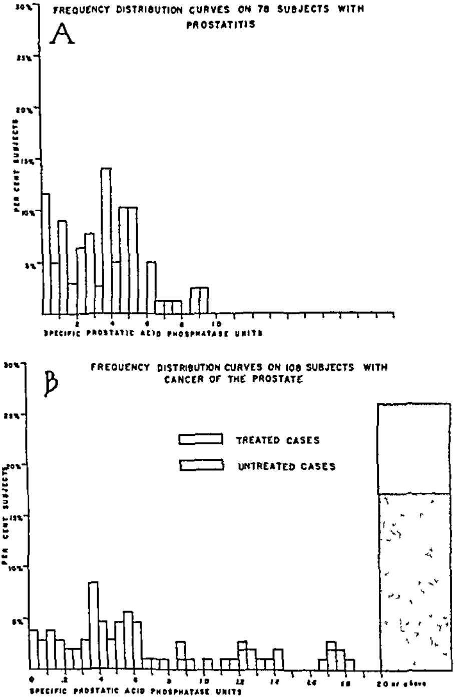

Fig. 2. *A*, frequency distribution curves on 108 subjects with prostatic cancer. Specific [illegible] distribution curves [illegible] units versus per cent subjects.

pancreas and skin cancer. The females bearing nonprostatic carcinoma had skin cancer, carcinoma of the tongue, cervical carcinoma and maxillary adamantinocarcinoma.

The 5 per cent false positives in the benign prostatic hypertrophy group (fig. 1, *D*) probably contain 60 per cent of subclinical carcinoma, but for the present must be classified as falsely positive in the absence of clinical signs, and cyto- or histodiagnosis.

Of a group of 8 positive cases studied in the Miami area which were also cytologically positive (class 4 and 5 cells) 5 were histologically confirmed.

The 8 per cent false positives in the prostatitis group (fig. 2, *A*) include both acute and chronic infections. Chronic infections superimposed on benign prostatic hypertrophy in elderly men also gave false positive values. Acute gonorrheal infection, or a history of previous gonorrhea, was present in many of the falsely positive group. In a large proportion of these cases, treatment was effective in lowering the values below 0.7 units. It is, of course, to be noted that 92 per cent of these subjects showed no elevation above 0.7 units.

The prostatic carcinoma group (fig. 2, *B*) showed no false negatives in this series except in treated cases. Treatment with estrogens very rapidly elicited negative values. It is impossible at present to predict how soon elevations would occur after withdrawal of estrogenic therapy, but indications are that elevation does not occur rapidly after withdrawal of estrogen therapy, especially if TACE has been administered. It is notable that some soft cancers of the prostate, which showed no clinically diagnostic signs, gave elevations above 0.7 units and in some cases gave values above 2.0 units.

DISCUSSION

Measurement of the tartrate inhibited portion of serum acid phosphatase by our newly developed method confirmed the findings of Fishman and Lerner that measurements based on tartrate inhibition were a more accurate measure of the prostatic fraction of serum. In a study involving 1106 subjects, our new method has proved simple and accurate. Early malignant lesions have been detected as predicted by the studies of the Tuft's group.

Elevations of specific prostatic acid phosphatase above 0.7 units in the serum show a high degree of correlation with untreated prostatic carcinoma. While there is some interference by false positives in nonmalignant disease and nonprostatic malignancy, these can be readily dealt with and correct diagnoses made eventually in most cases. The cases showing false positive values are patients with well defined, readily diagnosed disease. By therapy directed at correction of the nonmalignant or malignant disorder and repeated studies of specific prostatic acid phosphatase levels and prostatic cytology after the acute phases of the disorder have vanished, one can determine if the results were truly false positives. A male patient with unexplained persistent elevation of serum, specific prostatic acid phosphatase above 0.7 units *must be considered as possessing prostatic carcinoma until proved otherwise.*

Elevations above 1.3 units have been observed only in cancer bearing subjects in this series. There is a high degree of probability that these will be prostatic cancer. No elevations above 1.5 units have been observed in *any other disorder* except prostatic carcinoma.

Due to the widespread use of estrogen therapy, it is often difficult to ascertain the previous administration of estrogens especially in referred patients. In dealing with false negatives therefore, the clinician must not disregard clinical signs and cyto- or histodiagnosis.

The specific prostatic acid phosphatase test can be most usefully applied with our present state of knowledge if it is used in conjunction with present clinical cytological, radiological and histological methods. It should not be considered to replace any of these standard methods. Realistically, because of the simplicity of the method and because many patients do not have the benefit of application of all of the skills necessary for the diagnosis of prostatic carcinoma, the new method used alone as a screening device can accomplish much in the detection of prostatic carcinoma.

The accuracy figures quoted may be slightly changed by increasing the size of the series studied. Since the data were acquired by study of selected subjects, the results have bearing only on the accuracy of the method and must not be considered to represent figures that would be obtained by mass studies of the population. Further studies are in progress at present to extend the survey to 6000 subjects, to secure more exact accuracy figures, to determine the combined utility of cytology and specific prostatic acid phosphatase measurements in the *detection* of prostatic carcioma and to produce further refinements in the chemical method of estimation of specific prostatic acid phosphatase.

SUMMARY

Measurements of the tartrate inhibited acid phosphatase of serum utilizing nitrophenyl phosphate as a substrate have been performed in a uniform fashion by a new method on over 4000 subjects. Data on 1106 of these subjects, with complete clinical history, show a high degree of diagnostic ability for elevations of specific prostatic acid phosphatase above 0.7 units in the detection and diagnosis of carcinoma of the prostate.

General methods for exact diagnosis of patients showing elevations of specific prostatic acid phosphatase above 0.7 units, but lower than 1.5 units, have been developed. No patients without prostatic carcinoma, but with a great variety of nonmalignant and malignant disease showed an elevation above 1.5 units. Patients bearing elevations above this level can be considered to possess prostatic carcinoma with an exceedingly high degree of accuracy.

Wide experience through extensive co-operation with physicians, specialists and several institutions has demonstrated the usefulness of the method.

CONCLUSIONS

Specific prostatic acid phosphatase determinations have been performed on the sera of over 4000 subjects by a new, simple method.

The accuracy of the new method of determination has been demonstrated by bargraph distribution curves in 1106 subjects.

A tentative critical limit of 0.7 units has been set. Elevation above this value in a male patient is more closely related to prostatic carcinoma than to any other disease.

Elevations above 1.5 units have been observed in no other disease except prostatic carcinoma.

Tentative figures for accuracy of diagnosis of prostatic carcinoma have been described.

False negative diagnoses (values below 0.7 units) have thus far been found only in treated cases of carcinoma of the prostate.

The diseases and disorders responsible for false positive values have been described. Methods for the handling of this group to achieve more accurate diagnosis have been developed.

The utility of the specific prostatic acid phosphatase test for the detection and diagnosis of prostatic carcinoma has been defined.

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A CLINICAL, CYTOLOGICAL AND SEROLOGICAL APPROACH TO EARLY DETECTION OF PROSTATIC CANCER

PRELIMINARY REPORT

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A review of the voluminous literature on carcinoma of the prostate gland reveals that most articles express a common conception of the condition, namely, that it is futile, pessimistic, hopeless and sinister M Boyd and Nuckolls,[1] in 1940, after studying the literature extensively, stated that we had not progressed in the preceding 40 years, as far as control or cure is concerned, and further, that any hope of controlling or curing carcinoma of the prostate gland must be based on the discovery and diagnosis of the growth when it is small With this thought in mind, we ventured upon this research based upon a correlation of clinical, cytological and serological aspects of the disease, with the hope of establishing early diagnosis in a greater number of cases

The incidence of carcinoma of the prostate gland in men over the age of 50 has been estimated to be from 14 per cent to 46 per cent, (Rich[2], Baron and Angrist[3]) These estimates have been based on autopsy studies of large numbers of men, and in many instances numerous sections were taken from the same gland Kahler[4] reported 195 cases of postmortem examinations of prostatic carcinoma He found that 72 had been diagnosed clinically, 69 were diagnosed at necropsy alone, and 54 additional cases (13 9 per cent of 490 glands) by making more sections on cases that had been diagnosed benign, both clinically and pathologically He examined another series of 229 glands and reported 21 per cent carcinoma in men over the age of 50

Edwards[5] and co workers, in 81 routine autopsies, found latent carcinoma of the prostate in 14 8 per cent In 173 cases they found 16 7 per cent latent carcinoma in men over 40, and 3 4 per cent who had clinical carcinoma In Rich's series, the disease was recognized clinically in only 14 of 41 cases of carcinoma of the prostate Robert Moore[6] quoted the incidence as 16 7 per cent, with an increase to 29 per cent in the ninth decade

It is evident from these figures that there exists a great number of cases which

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Read at annual meeting, American Urological Association, New York, N Y June 1, 1954

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possess biologically inactive prostatic carcinoma, also referred to as latent or occult carcinoma, in which better methods of diagnosis must be developed and the inciting factors determined that render them biologically active. In nonmilitary practice, the number suitable for surgery, when diagnosed, varies from 5 to 13 per cent, a pitifully low percentage.

The inefficiency of the clinical diagnosis alone has been demonstrated. Many of the lesions found at necropsy measured no more than 4 mm. and were not palpable, even with the specimens in the pathologists' hands. Metastasis has too frequently occurred when malignancy is suspected by rectal palpation. Biopsy studies with the needle have been found wanting, and biopsy studies obtained at open surgery require a long processing technique for accuracy. Mulholland of the Mayo Clinic is quoted by Hock[7] and co-workers as having advocated cytologic studies as far back as 1931, only 3 years after Papanicolaou's discovery of cancer cells in the cervical secretion. These authors reported 150 cases, 13 of which had carcinoma of the prostate. Of the 13, there were four with positive cytologic smears and four with suspicious smears. They concluded that two positive cytologic smears were sufficient to institute surgery.

Edwards and co-workers[5] state that the average prostate contains about 63 tubules with branching acini. These are known to be lined with columnar or cuboidal epithelium, and although the carcinoma is usually located peripherally in the posterior or lateral lobes, the exfoliated cells may be discovered in the expressed secretion in a large number of cases, provided that the tubule is not blocked. Sometimes several cytologic studies are necessary before the cancer cells are demonstrated, and a negative cytology cannot prove the absence of cancer. G. G. Smith[8] found positive cell studies in 20 of 24 cases of carcinoma.

Peters[9] studied 341 cases, 72 of which had carcinoma of the prostate. Of these, 63 had positive cytology, 6 were suspicious and 3 negative.

In 1947, Herbut and Lubin[10] reported on cancer cells in prostatic secretion and found 17 positives in 100 patients. This was confirmed histologically in 10.

Before proceeding to the serological phase, it should be mentioned that there are technical factors involved in cytologic studies that render the specimen unsuitable. There should be a minimal amount of pus in the secretion collected, and when semen is milked from the vesicles with profuse spermatozoa, the specimen is not satisfactory, as it has been found that cancer cells are seldom found in these two instances. Albumin applied to the slide in a thin film before applying the secretion and immersing in the ether and alcohol has been found of great value in preventing the cells from washing off. Frosted glass slides are preferable and, lastly, an expert cytologist is essential.

A comprehensive report on the serological approach to diagnosis was presented

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[7] Hock, E. F., Wood, F. W. and Kosinski, A. A.: Cytologic detection of prostatic carcinoma; its clinical application. J. Urol., 63: 1081, 1950.

[8] Smith, G. G.: The treatment of carcinoma of the prostate. J. Urol., 64: 671, 1950.

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[10] Herbut, P. A. and Lubin, E. N.: Cancer cells in prostatic secretion. J. Urol., 57: 542–551, 1947.

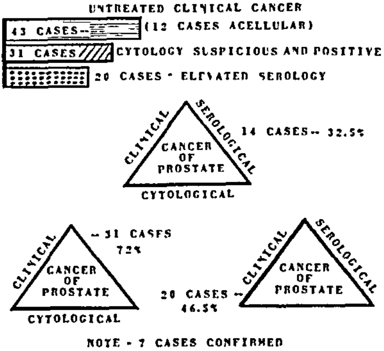

FIG. 1

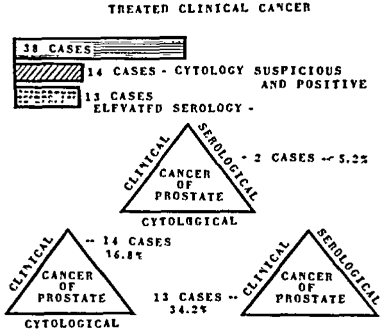

FIG. 2

by Fishman[11] and co-workers in 1953. They have applied the principle of separating the serum acid phosphatase derived from the prostate (P) from the total serum acid phosphatase (T). They quoted Bodansky and Bodansky in their review of the literature, that only 24 per cent of unselected patients without, and 81 per cent with bone metastasis from carcinoma of the prostate, show elevated serum acid phosphatase values. Fishman and Lerner, Abdul-Fadl and King, and others are quoted in their methods of separating the prostatic fraction to the exclusion of all other acid phosphatase. They report 12 cases of carcinoma of the prostate in their series, seven of whom had metastasis, and all seven had elevated total acid phosphatase and prostatic serum acid phosphatase. Five cases with no obvious metastasis showed elevated prostatic acid phosphatase in four and normal in one.

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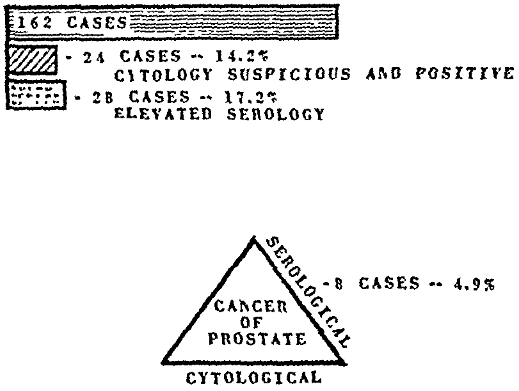
[11] Fishman, W. H., Dart, R. M., Bonner, C. D., Leadbetter, W. F., Lerner, F. and Homberger, F.. A new method of estimating acid phosphatase of prostatic origin applied to the clinical investigation of cancer of the prostate. J. Clin. Investig., 32: 1034–1044, 1953.

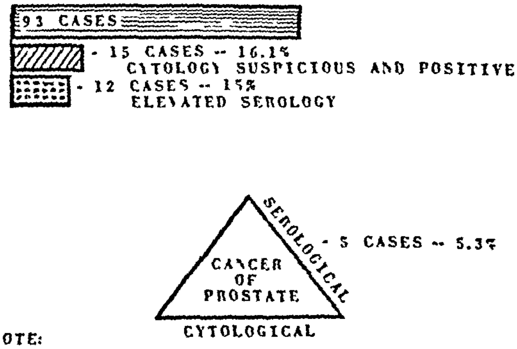
BENIGN PROSTATIC HYPERTROPHY



NOTE: 1 CASE CONFIRMED
1 CASE NOT CONFIRMED

FIG. 3

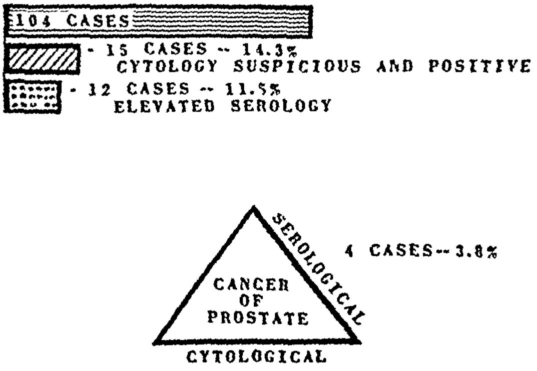
NO PROSTATIC DISEASE



NOTE:
6 CASES WITH ELEVATED SEROLOGY HAD LIVER DISEASE.
3 CASES CONFIRMED.

FIG. 4

PROSTATITIS



NOTE: 1 CASE CONFIRMED.

FIG. 5

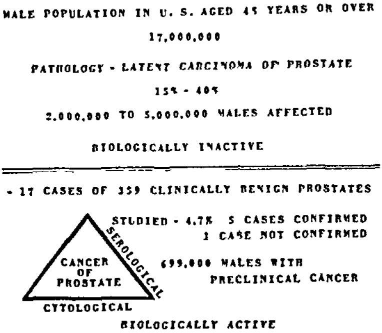

MALE POPULATION IN U. S. AGED 45 YEARS OR OVER
17,000,000
PATHOLOGY - LATENT CARCINOMA OF PROSTATE
15% - 40%
2,000,000 TO 5,000,000 MALES AFFECTED
BIOLOGICALLY INACTIVE
- 17 CASES OF 359 CLINICALLY BENIGN PROSTATES
STUDIED - 4.7% 5 CASES CONFIRMED
1 CASE NOT CONFIRMED
699,000 MALES WITH
PRECLINICAL CANCER
SEROLOGICAL
CANCER OF PROSTATE
CYTOLOGICAL
BIOLOGICALLY ACTIVE

FIG. 6

The values of (P) are constantly lower than (T) (expressed in King Armstrong units), and when published, they believed that a value of (P) greater than 0.5 showed an abnormal excess of the enzyme. The interpretation was expressed as tentative. The notion has become firmly fixed that elevated (T) is a measure of the metastatic process only, and even then its utility limited. This is a controversial idea at the present time, since normal prostatic cells excrete this enzyme, and carcinoma is not necessary to establish its presence. Fishman, et al. have shown that massage of the prostate elevates the serum acid phosphatase. It is further known that liver disease, gastro-intestinal upset, blood dyscrasias and gonorrhea might give abnormal estimates. We believe that chronic prostatitis will also give an elevated value in some instances. In our own series, hemolysis of the blood, heat and improper handling rendered many blood specimens unsuitable.

In co-operation with Dr. J. K. Cline,* Director of Cancer Research Department, Medical College of Alabama, School of Medicine, Birmingham, Alabama, who followed the principle of Abdul-Fadl and King, and later Fishman and Lerner, we have examined 440 cases of men over 40 years of age, from a combined clinical, cytological and serological standpoint, with the results appended in figures 1 through 6.

DISCUSSION

The prostate is anatomically so situated that it is in one of the most inaccessible parts of the body and, unlike carcinoma of the skin, cervix or breast, from which biopsy is easily obtained and the lesion can be visualized, prostatic carcinoma must be subjected to the diagnostic triad (clinical, cytological and serological) in order to increase early diagnosis.

One does not knowingly disseminate cancer cells by massage for fear of metastasis, but neither does one hesitate to massage the clinically benign gland in which a high percentage of unsuspected carcinoma exists and might be discovered early enough for corrective measures to be instituted.

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* After the preliminary cases, the serological studies were done by Dr. Thelma Gould, using Dr. Cline's method.

As tables 1 to 6 indicate, our results with specific prostatic acid phosphatase are not so efficient as Dr. Cline's. This is thought to be the result of improper handling of the specimens on our part. We have found that heat causes an elevation of the figure, and placing the whole blood next to the ice might result in hemolysis. There are numerous tedious steps in the chemical analysis and an expert chemist and specially trained technicians are desirable.

The factors influencing false results must be eliminated by the internist in many instances. It is our opinion that the family physician can initiate the cytology and serology and should be encouraged to perform more rectal digital examinations in the routine physical examination.

It is our contention that diagnosis of carcinoma of the prostate might be made by any two sides of the triad; *however, the standards of treatment for various* combinations of the triad (which are not a part of this presentation) must be weighed and established after prolonged study over a period of years, and no *doubt there will continue to be controversy, as there has been in the past, as to* proper management.

SUMMARY AND CONCLUSIONS

A preliminary report is presented on 440 patients above the age of 40, who were subjected to clinical, cytological and serological investigation in an effort to detect cancer of the prostate.

Our results are presented in the illustrations.

Many cases in which we found positive cytology were clinically benign, indicating the presence of biologically inactive cancer or an early active lesion.

The elevated prostatic serum acid phosphatase (0.7 or higher King Armstrong units) is thought to mean biological activity unless caused by one of the conditions mentioned in the text that produced false positives.

It is our opinion that more cases of early carcinoma of the prostate will be suspected or diagnosed if all patients in the proper age range are subjected to cytological and serological study in addition to palpation. Prostatic serum acid phosphatase is more critical than total serum acid phosphatase and promises to aid materially in diagnosis or activity of prostatic carcinoma, but we feel that it must be made more specific than it is at present.

Cytologic examination of prostatic fluid is of definite value in detecting a greater number of early cases.

Therapy is not discussed in this paper; however, we would be remiss in closing without warning against androgenic drugs in those cases that are clinically benign but show positive cytology or elevated acid phosphatase.

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THE ROLE OF THE ADRENAL CORTEX IN PROSTATIC CANCER

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The rationale of bilateral total adrenalectomy in the treatment of patients with advanced prostatic cancer is based on the hypothesis that removal of these glands eliminates the major, if not the only, remaining source of extragonadal androgens after castration, thereby depriving androgen-dependent tumors of a continuing supply of these hormones Inasmuch as certain prostatic cancers have been postulated to be independent of androgens,[1] West and his co-workers believe that the beneficial effect of adrenalectomy may be due to a nonspecific alteration in the hormonal environment [2] Dobriner and his group have shown abnormal amounts and types of steroids in the urine of patients with a variety of neoplastic diseases [3]

Various investigators have reported their experiences with bilateral total adrenalectomy in patients with advanced prostatic cancer [2, 4, 5, 6, 7, 8] In a considerable number of these cases striking subjective improvement has been observed and, in a few instances, temporary inhibition of the tumor growth has been reported Inasmuch as the operation has apparently not been curative in any of the cases reported, the ultimate value of bilateral adrenalectomy in the treatment of advanced prostatic cancer is still a subject for further study

Available reports indicate that, hitherto, adrenalectomy has been reserved for patients with advanced, disseminated carcinoma of the prostate, who have relapsed following castration and estrogen therapy To our knowledge, the use of adrenalectomy in the earlier stages of the disease has not been reported

During the past 2 years a detailed study of the effect of adrenalectomy in prostatic cancer has been in progress on the Fourth Division Urology Service of

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Read at annual meeting, American Urological Association, New York, N Y June 2, 1954

This work was made possible by a Grant in-Aid from the American Cancer Society upon recommendation of t[illegible] [illegible] onal Research Council, and by a research [illegible] [illegible] ellowships of the National Insti[illegible]

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Bellevue Hospital and the Urology Service of the University Hospital of the New York University-Bellevue Medical Center, in association with the Urology Research Laboratory of the New York University Post-Graduate Medical School, and the Department of Chemistry of the New York University College of Medicine. We are reporting herewith our initial observations on the effects of bilateral adrenalectomy in 20 patients with advanced prostatic cancer, with or without demonstrable metastasis. On rectal palpation, the local process had apparently extended beyond the confines of the gland in all of the patients. A positive tissue diagnosis was obtained in every instance, either via open perineal exposure of the posterior aspect of the gland, or from specimens removed during the course of prostatic surgery. Bilateral adrenalectomy was carried out in 11 patients who had relapsed following castration and estrogens, and in nine who had never received any previous therapy whatsoever. The latter group provided an opportunity to study the role of the adrenal cortex *per se* in prostatic growth.

CASE MATERIAL AND METHODS

Twenty patients with cancer of the prostate were selected from the Fourth Division Urology Service of Bellevue Hospital and the Urology Service of the New York University Hospital. The clinical data in these cases are summarized in table 1. The ages ranged from 47 to 76 years, the median age being 63. Exten-

TABLE 1. *Clinical status prior to bilateral adrenalectomy*

No.	Patient	Age	Extent of Disease*		Symptoms			
			Skeletal metastasis	Pulmonary metastasis	Pain	Vesical obstruction	Weight loss	Previous orchiectomy and estrogens
1.	A. M.	47	+	+	+	Complete	+	+
2.	M. C.	60	0	0	+	Complete	+	+
3.	M. D.	58	0	0	+	Partial	+	0
4.	G. K.	65	+	0	+	Partial	+	+
5.	A. S.	71	0	0	+	Complete	+	0
6.	E. F.	60	+	0	+	Complete	+	+
7.	O. P.	60	0	0	+	Partial	+	+
8.	J. L.	63	+	0	+	Complete	+	0
9.	M. M.	63	+	+	+	Complete	+	0
10.	G. B.	59	+	+	+	Partial	+	+
11.	F. R.	76	+	0	0	Partial	+	0
12.	J. H.	73	+	0	0	Partial	+	+
13.	E. B.	65	+	0	0	Partial	+	0
14.	G. B.	71	+	0	0	Partial	+	+
15.	J. B.	69	+	0	0	Complete	+	+
16.	G. C.	62	+	0	0	Complete	+	0
17.	C. H.	71	+	0	+	Partial	+	0
18.	R. M.	60	0	0	0	Partial	+	+
19.	J. N.	49	+	0	+	Partial	+	+
20.	S. S.	71	0	0	0	Complete	+	0

* Primary growth had extended beyond the confines of the gland in all cases, on rectal palpation.

sive osseous metastasis were present in 14 patients (cases 1, 4, 6, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 19) three of whom (cases 1, 9, 10) also exhibited pulmonary metastasis. Twelve patients (cases 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 17, 19) complained of pain as a major symptom, varying in degree from localized perineal pain (cases 3 and 7) to severe metastatic pain requiring frequent injections of narcotics (cases 2, 4, 6, 19). Symptoms of vesical neck obstruction were present in all. Nine were in complete urinary retention at the time of admission to the hospital (cases 1, 2, 5, 6, 8, 9, 15, 16, 20) while the rest had varying degrees of prostatism. Weight loss was exhibited by all.

Eleven patients (cases 1, 2, 4, 6, 7, 10, 12, 14, 15, 18, 19) had been subjected to orchiectomy and treated by estrogens before adrenalectomy. Castration was performed more than 24 months prior to adrenalectomy in 3 patients (cases 1, 7, 14), 12 to 24 months earlier in three (cases 2, 6, 10) and less than 12 months earlier in five (cases 4, 12, 15, 18, 19). Estrogen treatment had been instituted thereafter and subjective improvement invariably noted. At the time of adrenalectomy all of these patients were in the stage of relapse following hormonal therapy.

Nine patients were subjected to bilateral adrenalectomy as initial therapy. Seven of these (cases 3, 5, 8, 9, 11, 13, 16) were subsequently castrated, while the remaining two (cases 17 and 20) have received no other treatment to date.

Operative technique. Removal of the adrenal glands was performed in two stages, the second gland being removed 2 weeks after the first. The adrenal was exposed extrapleurally, with resection of segments of the eleventh and twelfth ribs. The use of silver clips to control bleeding materially shortened and simplified the operation.

Pre- and postoperative care. The regimen followed was essentially similar to that outlined by Huggins and Bergenstal.[9] Cortisone, 200 mg., in divided doses and desoxycorticosterone acetate, 5 mg., were administered on the day before operation. An additional 150 mg. cortisone and 5 mg. desoxycorticosterone acetate were given an hour before operation. During and after the operative procedure a norepinephrine drip was administered intravenously whenever the systolic blood pressure fell to below 100 mm. Hg. Fifty mg. cortisone were given every 4 hours during the immediate postoperative period, and lessened gradually until a daily maintenance dose of 25–50 mg. had been attained by the tenth day. Desoxycorticosterone acetate was discontinued by the end of the first week postoperatively, none being required for maintenance therapy.

It must be pointed out that the foregoing preoperative measures were instituted prior to the first stage operation and again before the second. It has been our experience, as well as that of others, that unsuspected hypofunction may exist in the remaining adrenal, for one reason or another. Two of our patients, for example, were found to have extensive replacement of both adrenal glands by metastatic prostatic cancer, which was not apparent on gross inspection of the specimens at the time of operation. Each developed marked hypotension following the first stage, necessitating continuous norepinephrine and additional cortisone before the blood pressure could be restored to normal. Adequate preparation with cortisone and desoxycorticosterone acetate seems warranted prior to the removal of the first adrenal.

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[9] Huggins, C. and Bergenstal, D. M.: Surgery of the adrenals. J. A. M. A., 147: 101–106, 1951.

Blood samples for electrolyte studies were obtained every three days during the first two weeks after operation, and once weekly thereafter until discharge from the hospital. Deviations from the normal plasma values for sodium and potassium were corrected by altering the dosage of cortisone and desoxycorticosterone, and replacing or withholding sodium and potassium, as indicated.

Follow-up studies. The patients were seen every 2 weeks in the out-patient department. During these visits any subjective changes were noted and body weights recorded periodically. Serial determinations of serum acid phosphatase and urinary 17-ketosteroids were obtained. Roentgenograms of the bone lesions were repeated at regular intervals. The patients were usually maintained adequately with 25–50 mg. cortisone daily, desoxycorticosterone not being required. During the summer months the patients were advised to take an additional 3–5 gm. sodium chloride daily.

RESULTS

The clinical responses observed in the twenty patients with cancer of the prostate treated with bilateral total adrenalectomy have been summarized in table 2. One patient (case 1) died 8 days and another (case 19) four days after the removal of the second adrenal, thus leaving 18 cases for critical evaluation.

Relief of pain. Of 10 patients who initially complained of pain, complete relief resulted in four (cases 3, 6, 7, 17), partial in five (cases 2, 5, 8, 9, 10), and none in one (case 4). The most striking improvement was observed in case 6, in which the patient had previously required frequent injections of morphine because of severe pain attributable to extensive metastasis. Shortly after removal of both adrenal glands he became completely comfortable and has not required further sedation. Although not as dramatic, but equally impressive are the results in case 17, who also had suffered intense pain prior to adrenalectomy. The pain continued unabated after adrenalectomy and he was discharged unimproved. The pain subsequently lessened and by the eighth month, he was without symptoms and able to resume his former activities. Cases 3 and 7 had marked perineal pain which was also alleviated. Five patients obtained partial but transient relief of pain after adrenalectomy. Adrenalectomy was of no benefit in case 4, who had severe pain due to widespread skeletal metastasis.

Vesical obstruction. Symptoms of urinary obstruction were lessened in 9 patients (cases 2, 4, 6, 7, 12, 14, 15, 17, 18) and unrelieved in 9 patients (cases 3, 5, 8, 9, 10, 11, 13, 16, 20) after adrenalectomy. Continuous catheter drainage was necessary in all patients to facilitate steroid and electrolyte excretion studies, thereby making it difficult to evaluate any changes in urinary symptomatology. It may be significant, however, that three (cases 2, 6, 15) of the group who improved following adrenalectomy had been in complete urinary retention prior to operation. Six patients (cases 3, 5, 8, 11, 13, 20) required transurethral resec-

TABLE 2. *Clinical response to bilateral adrenalectomy*

No.	Patient	Relief of Pain	Obstruction Removed	Regression of Local Lesion	Regression of Bone Lesion	Gain in Weight	Survival Time	Present Status	Cause of Death
1.	A. M.	—	—	—	—	—	15 days	Dead	Postoperative adrenal insufficiency
2.	M. C.	Partial	Lessened	No	*	No	6 mos.	Dead	Carcinoma
3.	M. D.	Complete	No	No	No	Yes	24 mos.	Living	
4.	G. K.	None	Lessened	No	No	No	6 mos.	Dead	Carcinoma
5.	A. S.	Partial	No	No	*	Yes	16 mos.	Living	
6.	E. F.	Complete	Lessened	No	No	No	5 mos.	Dead	
7.	O. P.	Complete	Lessened	Yes	*	Yes	13 mos.	Living	
8.	J. L.	Partial	No	No	No	No	3 mos.	Dead	Mesenteric thrombosis
9.	M. M.	Partial	No	No	No	No	2 mos.	Dead	Carcinoma
10.	G. B.	Partial	No	No	No	No	2 mos.	Dead	Carcinoma
11.	F. R.	*	No	No	No	No	2 mos.	Dead	Undetermined
12.	J. H.	*	Lessened	No	No	Yes	13 mos.	Living	
13.	E. B.	*	No	No	No	Yes	13 mos.	Living	
14.	G. B.	*	Lessened	No	No	No	9 mos.	Living	
15.	J. B.	*	Lessened	No	No	No	10 mos.	Living	
16.	G. C.	*	No	No	No	Yes	10 mos.	Living	
17.	C. H.	Complete	Lessened	No	No	Yes	10 mos	Living	
18.	R. M.	—	Lessened	No	No	No	7 mos.	Living	
19.	J. N.	—	—	—	—	—	4 days	Dead	Postoperative adrenal insufficiency
20.	S. S.	*	No	No	No	No	2 mos.	Living	

— Inadequate period of observation.
* Corresponding symptom absent prior to adrenalectomy.

tion of the prostate before satisfactory voiding could be achieved. Case 16 was in complete retention prior to adrenalectomy and remained so for 1½ months after adrenalectomy, necessitating continuous catheter drainage. Bilateral orchiectomy was then carried out, and he subsequently was able to void with ease. The remaining unimproved patients (cases 9 and 10) failed rapidly, and remained on catheter drainage until their deaths.

Weight change. Seven patients (cases 3, 5, 7, 12, 13, 16, 17) showed significant gains in body weight, without clinical evidence of edema. Four of this group (cases 12, 13, 16, 17) had widespread bony metastasis. The serial body weights of five of these patients are illustrated in figure 1, *A*. The remaining 11 patients showed no improvement in this regard. A remarkable increase in body weight occurred in patient 12 who had been steadily losing weight despite previous castration and continued estrogen treatment. Despite extensive metastasis, his weight increased remarkably after adrenalectomy, and he has recently been forced to employ a reducing diet, so far without success.

Regression of local and metastatic lesions. Only one patient (case 7) showed definite regression of the local growth. Cancer had been discovered quite unexpectedly in the surgical specimen removed after simple perineal prostatectomy 2 years earlier. Castration had been performed at that time, and supplemented with estrogen treatment. He was re-admitted because of perineal pain and progressively enlarging nodular recurrence of his local lesion. Following bilateral adrenalectomy definite regression in the size of his lesion was noted, together with a disappearance of pain.

No regression in the osseous metastasis has been observed in any of the pa-

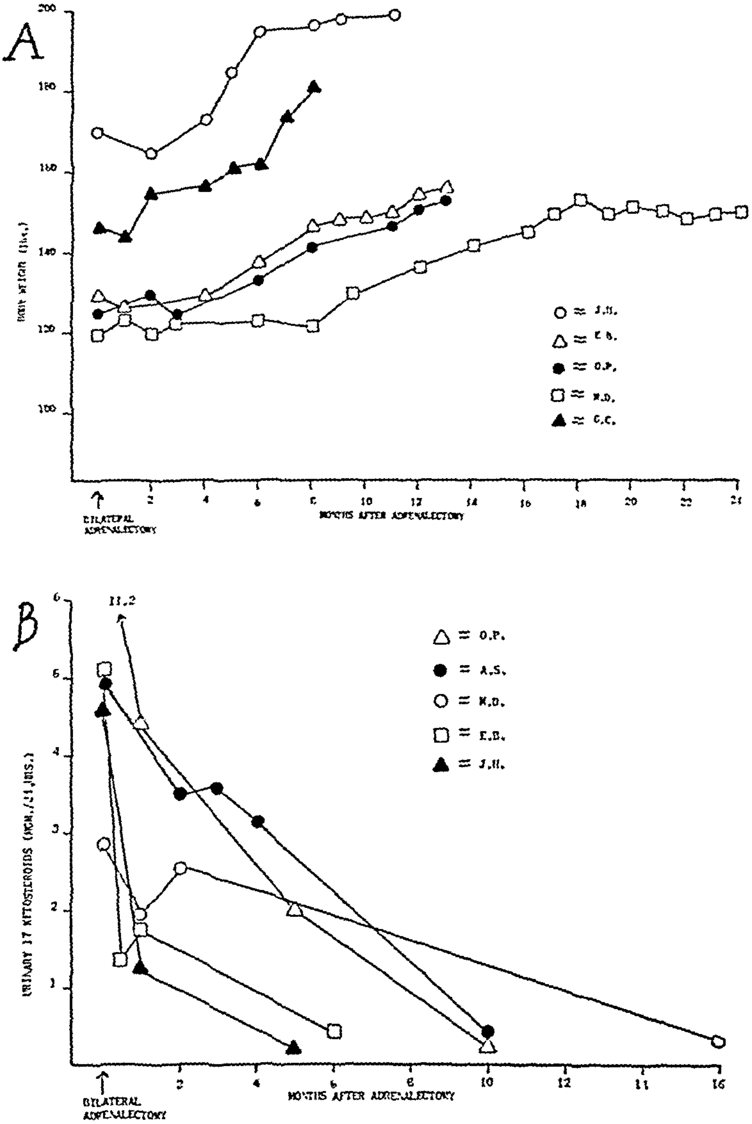

FIG. 1. *A*, effect of bilateral total adrenalectomy on body weight. *B*, effect of bilateral total adrenalectomy on urinary 17-ketosteroid excretion.

tients, as judged from the x-ray findings Rather, we have observed actual increase in the extent of osseous deposits in several patients

Survival time Eleven of the twenty patients (cases 3, 5, 7, 12, 13, 14, 15, 16, 17, 18, 20) are alive at the present time, the longest follow-up being 24 months (case 3) Five patients (cases 3, 5, 7, 12, 13) are alive more than a year after bilateral adrenalectomy, another five (cases 14, 15, 16, 17, 18) from 6 months to 1 year, and one (case 20) less than six months Two patients (cases 1 and 19) died of postoperative adrenal insufficiency Patient 8 suffered a mesenteric thrombosis, to which he succumbed Four patients (cases 2, 4, 9, 10) died from progression of their disease The causes of death in the remaining two (cases 6 and 11) were not ascertained

Effects of pre castrational adrenalectomy The results of bilateral adrenalectomy in nine previously untreated patients, and before any were subjected to orchiectomy, are summarized in table 3 The periods of observation ranged from 20 to 300 days Urinary obstruction was lessened in one Five patients in this group had suffered intractable pain prior to adrenalectomy Two were subsequently completely relieved, and three partially relieved of their pain There was a significant increase in body weight in 4 patients without clinical evidence of edema No regression of local or metastatic lesions was ever observed

Two case reports are herewith submitted:

Case 1 E B (B H 10478 53), a 65 year old Negro male, was admitted to Bellevue Hospital on March 3, 1953, with a 1 year history of progressive increase in urinary frequency, dysuria and nocturia He had lost 20 pounds of weight but there was no bone pain The residual urine on admission was 500 cc Rectal palpation revealed marked enlargement of the prostate with fixation and firmness on the right side The area of induration extended into both seminal vesicles A skeletal series demonstrated osteoblastic metastasis in the dorsal vertebrae, ribs, pelvis, and femora The chest x-ray was negative

A biopsy of the prostate was obtained by perineal exposure in March 1953, histological examination showed adenocarcinoma Bilateral total adrenalectomy was performed in two stages in April 1953 Rectal examination 1 month following adrenalectomy showed no diminution in the size of the prostate The pa-

TABLE 3 *Effect of bilateral adrenalectomy alone (no castration or estrogens)*

Patient	Period of Observation	Relief of Obstruction	Pain Relief	Tumor Regression	Weight Gain
M D	84 days	None	Complete	None	10 lbs
A S	48 days	None	Moderate	None	15 lbs
J L	36 days	None	Moderate	None	None
M M	46 days	None	Moderate	None	None
F R	33 days	None	*	None	None
E B	249 days	None	*	None	20 lbs
G C	20 days	None	*	None	None
C H	330 days	Partial	Complete	None	45 lbs
S S	100 days	None	*	None	None

* Corresponding symptom absent

tient's urinary symptoms remained unchanged. A transurethral resection of the prostate was thereupon performed 4 weeks following removal of the second adrenal. At the same time the right testis was removed for histological study for possible post-adrenalectomy effect. When discharged from the hospital, the patient was given a maintenance dose of 25 mg. cortisone twice daily.

During the next 8 months, the patient improved steadily. His weight increased from 122 to 148 pounds, and he felt considerably better. He continued to void satisfactorily and had no urological complaints. The intact left testis showed no gross changes in size or consistency and presumably continued to function as before.

In November 1953, the remaining testis was removed. No remarkable clinical change has been observed since the testes were removed. At the present time the patient is gainfully employed and apparently quite comfortable. Histological studies of routine sections of the testes have shown no unusual changes which might be ascribed to absence of the adrenals.

Case 2. C. H. (U.H. 67726), a 71 year old Negro, was admitted to University Hospital on May 25, 1953, because of severe pain in his hips, thighs, shoulders, and head for 6 months. A weight loss of 20 pounds had occurred following the onset of pain. There were no urinary difficulties except for some nocturia. Rectal examination disclosed marked enlargement of the prostate, with stony-hard nodularity in the right lobe and extension in the region of the seminal vesicles. X-rays showed osseous metastasis to the ribs, pelvis, spine and femora. The chest x-ray was negative.

Histological examination of prostatic tissue removed by open perineal biopsy in May 1953 showed cancer. A two-stage bilateral adrenalectomy was done in June 1953. The patient remained in the hospital 1 month following adrenalectomy. During this time he experienced no relief from his pain and his condition seemed to deteriorate steadily. It was felt that adrenalectomy had not been beneficial. At the time of discharge, he was receiving 25 mg. cortisone twice daily for maintenance and virtually bed-ridden.

The patient was not seen again for 4 months, at which time he returned for follow-up studies. To our surprise, he exhibited remarkable improvement. He had gained 45 pounds in weight, was practically free of pain, and ambulated without discomfort. The patient stated that shortly after leaving the hospital, his physician had begun estrogen treatment with TACE capsules. He remained on this regimen 2 months longer, for a total of 6 months. TACE was then discontinued, cortisone being given as heretofore. Four months have elapsed since the estrogen therapy was discontinued, and the patient remains well.

Urinary 17-ketosteroids. Changes in the levels of 24 hour urinary 17-ketosteroids following adrenalectomy in 5 cases are depicted in figure 1, *B*. The values represent the average obtained in three consecutive 24 hour determinations run in duplicate fashion. The preoperative excretory levels range from 2.9 to 5.1 mg. per 24 hours in four of these patients. These values are within the normal limits expected for individuals in this age group. The value in patient, O.P. (case 7), however, was 11.2 mg. per 24 hours. He had had a previous orchiectomy and sub-

TABLE 4. *Results of bilateral adrenalectomy for advanced prostatic cancer*

	No of Cases	Subjective Improvement	Objective Improvement
Huggins et al. 1952	7	5	0
Scott et al. 1953.	2	1	0
Baker 1953	10	8	0
Scardino et al. 1953.	3	2	1
Taylor et al. 1953	6	5	1
Harrison et al. 1953	7	5	1
Randall et al.	17	11	2

sequent pathological examination of the adrenals showed adenomatous changes in both adrenal cortices, which may account for the elevation in his urinary 17-ketosteroid level. Following adrenalectomy, the 24 hour excretory totals decreased in all patients, but never disappeared completely.

DISCUSSION

Our studies indicate that bilateral total adrenalectomy provides certain limited benefits for patients with advanced prostatic cancer. This is in essential agreement with other observers. (See table 4.) Subjective improvement, while usually not as dramatic as that which follows castration or estrogen therapy, occurs in about half the patients.

Of interest is our observation that the clinical response in patients subjected to adrenalectomy before castration does not differ remarkably from that seen in the post-castration group. Our findings in this regard may be compared with those of Huggins and Dao in a series of 50 women with breast cancer, in whom it was reported that bilateral adrenalectomy alone benefited as many patients as simultaneous bilateral adrenalectomy and oophorectomy.[10] Our observation in this regard may lend credence to the view that the beneficial effects of castration, estrogen administration, adrenalectomy or even hypophysectomy in prostate cancer are better ascribed to the sudden induction of an endocrine imbalance in the body, rather than to any specific anti-androgenic effect.[11] This seems to be supported by observations that testosterone and progesterone occasionally have actually improved patients with advanced, metastatic prostatic cancer.[12]

One of the arguments against adrenalectomy in the treatment of prostatic cancer has been that cortisone and hydrocortisone, either of which is essential for the maintenance of life postoperatively, have been shown to be metabolized in man into at least one product with androgenic potency, namely, 11-hydroxyandrosterone.[13] Thus, the replacement therapy itself may partially nullify the primary objective of adrenalectomy, which is the elimination of androgens from the body. Recent work, however, has shown that elevations of urinary androgen titers do not occur on the usual maintenance doses of cortisone (25–50 mg. per day). It is only when cortisone dosage has been increased to 100–300 mg. per day (for investigative purposes), that increases in androgen excretory levels above preoperative values are observed.[14] Furthermore, corticosterone (compound B), which is apparently capable of supporting life after total adrenalectomy, has been found to be a much less potent precursor of androgens and 17-ketosteroids than either compounds E or F. This compound is presently being evaluated as replacement therapy after adrenalectomy.

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[10] Huggins, C. and Dao, T. L.: Adrenalectomy and oophorectomy in treatment of advanced carcinoma of the breast J. A M. A., 151: 1388–1394, 1953.

[11] Randall, H. T.: *An evaluation of adrenalectomy in man: Physiological changes and the effect on advanced neoplastic disease.* Bull. N. Y. Acad. Med., 30: 278–301, 1954.

[12] Brendler, H., Chase, W. E. and Scott, W. W. Prostatic cancer Further investigation of hormonal relationships. Arch. Surg , 61: 433–440, 1950

[13] Pearson, O. H., Whitmore, W. F., West, C. D., Farrow, J. H. and Randall, H. T.: Clinical and metabolic studies *of bilateral adrenalectomy.* Surgery 34: 543–555, 1953

It is possible that adrenalectomy may improve the clinical response to estrogens in previously resistant cases.[15] Patient 17, after having demonstrated no improvement following adrenalectomy, responded extremely well to a 4 month course of TACE, and has remained well for 4 months since cessation of estrogen therapy. This may represent another example of beneficial effects induced by a nonspecific disturbance in the endocrine equilibrium in the body.

At the present time most observers believe that bilateral adrenalectomy offers too little to justify its continued use in the treatment of the advanced stages of carcinoma of the prostate. The operation affords only limited subjective improvement which is probably transient at best. Objective regression occurs but infrequently, when compared, for example, with that seen in patients with breast cancer.

We are not prepared to accept these views completely, in the light of our studies to this time. Bilateral adrenalectomy has been shown to provide a definite measure of subjective relief in at least 40–50 per cent of patients who would otherwise remain in a state of relapse until their deaths. Moreover, in our hands it has proved to be a comparatively safe and simple procedure in patients who are suitable surgical risks. Postoperative maintenance with cortisone is quite satisfactory. The conversion of this steroid into compounds with androgen potency is probably not significant on the usual postoperative dosages. It is our feeling that adrenalectomy should be performed in suitable patients who have relapsed after castration and estrogen administration. Although we are continuing to perform total adrenalectomy before castration in some of our patients as part of a study of adrenal:testis relationships, we do not recommend this procedure for routine use in the clinical management of patients with advanced prostatic cancer.

SUMMARY

The effects of bilateral total adrenalectomy in 20 patients with advanced prostatic cancer, with or without secondary dissemination of the disease, are reviewed. Bilateral adrenalectomy was performed in 11 patients who had relapsed following castration and estrogens. The remaining nine had intact testes and had never received estrogen therapy prior to adrenalectomy. The latter group pro-

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[14] Munson, P. L., Goetz, F. C., Laidlaw, J. C., Harrison, J. H. and Thorn, G. W.: Effect of adrenocortical steroids on androgen excretion by adrenalectomized orchidectomized men. J. Clin. Endocrinol. & Metab., **14**: 495–508, 1954.

[15] Scardino, P. L.: Personal communication.

vided an opportunity to study the role of the adrenal cortex *per se* in prostatic growth

Eighteen patients were available for critical evaluation Eleven are still alive Of 10 patients who complained of pain initially, complete relief was experienced by four, partial in five and none in one Symptoms of urinary obstruction were lessened in 9 patients and unrelieved in nine Seven patients showed significant increases in body weights, despite the presence of extensive metastasis in four A regression in the local growth was noted in one patient No regression of the osseous metastasis as judged by x-ray findings was observed in any of the patients

A comparison of the clinical response observed in patients subjected to pre- and post castration adrenalectomy shows no remarkable difference in the two groups

Bilateral adrenalectomy has been shown to provide a definite measure of subjective relief in at least 40 – 50 per cent of patients who otherwise would remain in a state of relapse until their deaths The procedure has also proved to be a safe and simple procedure in patients who are reasonable surgical risks It is our feeling that adrenalectomy should be performed in suitable patients who have relapsed after castration and estrogen administration.

The authors are indebted to Drs Sydney Gordon and Benjamin Peng and Mrs Joyce Abbott O'Flaherty for their assistance in this work

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RADIOACTIVE CHROMIC PHOSPHATE IN TREATMENT OF UROLOGICAL TUMORS

VINCENT MOORE, DEAN GAMBLE, B.S., RAYMOND L. LIBBY, PH.D. AND WILLARD E. GOODWIN

From the Departments of Surgery/Urology and Radiology, University of California Medical Center, Los Angeles

This is a report of the first 25 cases of inoperable prostatic and bladder carcinoma treated by manual, interstitial injection of radioactive chromic phosphate by the Division of Urology and the Department of Radiology of the UCLA Medical School in conjunction with the Radioisotope Unit of Wadsworth General Hospital of the Veterans Administration Center at Los Angeles.

The treatment of urologic tumors by interstitial injection of radioactive, insoluble salts has progressed rapidly since atomic piles made a wide variety of isotopes available after World War II. Following the pioneer studies of Flocks[1] with radioactive colloidal gold in the treatment of inoperable prostatic carcinoma, safer and more effective sources of interstitial radiation have been sought by many workers. Rusche was the first to use radioactive chromic phosphate for the treatment of inoperable prostatic carcinoma.[2] Other isotopes are now under study for their radiation effectiveness and safety.

In March 1953, our study was undertaken to evaluate the effectiveness and safety of radioactive chromic phosphate in various urological tumors. The program has required a closely organized team of radiation physicists, isotope research laboratory personnel, radiologists, pathologists and urologists. Without the simultaneous mutual assistance of all these groups, the study project could not function with any degree of safety or scientific accuracy.

Radioactive chromic phosphate was chosen as the source of tumorcidal radiation at the radiation physicist's suggestion. There seem to be two main advantages in using this isotope instead of gold. Radioactive colloidal gold emits both beta and gamma radiation. This gamma component puts it in the same radiation hazard class as radium and radon therapy. Radiation effects from exposure are cumulative, the body "storing" radiation effects it is exposed to over the years. Continual exposure of doctors, nurses and other hospital personnel to repeated gamma radiation from gold (either while handling the isotope at surgery or in the postoperative care of the patient) is a serious problem even when heavy lead shielding is used in conjunction with an effective safety monitoring program for work areas. Radioactive phosphorus, on the other hand, is a pure beta emitter. These beta particles are readily absorbed in a few millimeters of glass, leucite or tissue.

A second advantage accrues to the *patient* receiving isotope treatment. Because

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Read at annual meeting, Western Section of American Urological Association, Victoria, B. C. April 19–22, 1954.

Aided by grants from the Bay District Surgical Research Fund and the Fund for the Advancement of Urology.

[1] Flocks, R. H., Kerr, H. D., Elkins, H. B. and Culp, D.: Treatment of carcinoma of prostate with interstitial irradiation with radioactive gold (Au^{198}): A preliminary report. J. Urol., **68:** 510–522, 1952.

Flocks, R. H.: Treatment of carcinoma of the prostate. J. Urol., **70:** 491–498, 1953.

[2] Rusche, Carl and Jaffe, H. L.: J. Urol., **72:** 466–476, 1954.

TABLE 1. *Physical characteristics of radioactive phosphorus and gold*

	Phosphorus	Gold
Maximum energy of emitted beta ray	1.71 mev.	.97 mev
Gamma ray energy	*none*	0.411 mev.
Range of beta ray of *maximum* energy in tissue	8.0 mm.	4.0 mm.
Volume of sphere of radius equal to *maximum* beta ray range	2.14 cm.^{3}	0.27 cm.^{3}
Average energy of emitted beta ray	0.695 mev.	0.32 mev.
Range of particle of *average* energy	3.2 mm.	.069 mm.
Volume of sphere of radius equal to *average* energy range of beta ray	137 cm.^{3}	.003 cm.^{3}
Dosage delivered to one gram of tumor tissue by one microcurie of isotope in rep. (*) over total decay[3]	885 rep/μc/gm	76 rep/μc/gm.
Number of microcuries deposited in one gram of tissue to derive 88,500 rep. over total decay	100	1092
Half life	14.5 days	2.7 days
Particle size	0.25–0.5 microns	0.002–0.007 microns

* rep. means roentgen equivalents physical, which approximates roentgens in usual x-ray dosage practice.

of the absence of gamma radiation and the limited penetration of the beta radiation in tissue (a maximum of 8 mm.), radioactive phosphorus can be placed close to the edge of tumor tissue with less risk of injury to adjacent vital viscera or blood vessels.

Table 1 compares the significant physical characteristics of radioactive phosphorus and gold.

One important objective in this study was to observe what a standard dosage of interstitial irradiation per gram of tumor tissue would accomplish. Accurate information on the effects of varying doses of interstitial irradiation on benign and malignant tissues is scanty in the literature. There are little published data on which to base dosage for either gold or phosphorus in genito-urinary cancers. Radioactive chromic phosphate injection of external, superficial tumors of the face, mouth and throat has been studied with doses as low as 10,000 rep. per gram of tumor tissue.[4] In these facial tumors, the dosage was increased to 80,000 rep. per gram of tumor when inadequate tumorcidal effect of lower doses was observed. Therefore, in urological tumors a dose of 100 microcuries of P^{32} per gram of tumor was chosen and adhered to in all these cases. This dose when allowed to totally decay in one gram of urological tumor tissue will deliver 88,500 rep. (roentgen equivalents physical).

From careful and repeated studies in dog prostates it was shown that one

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[3] Marinelli, L. D., Quimby, E. H. and Hine G. H.: Dosage determination with radioactive isotopes II Practical considerations in therapy and protection. Am. J. Roentgenol. & Rad. Therapy, 59: 260–281, 1948.

[4] Mumma, C. S.: Treatment of mixed tumor of tongue with radioactive chromic phosphate solution. A. M. A. Arch. Otolaryngol., 58: 192–195, 1953.

TABLE 2

	Died	Living with Cancer	Living with Negative Biopsy
Prostatic cancer	3	4	7
Bladder cancer	7	1	3

gram of tissue would easily retain 0.1 ml. of injected fluid and in some cases 0.2 ml. of fluid. Larger volumes per gram of tissue were accompanied by increased leakage of the isotope fluid from tissue.

This report summarizes the first 25 patients manually injected with isotope using an ordinary glass syringe. These were all cases of inoperable prostatic and bladder carcinoma. These patients have been followed for a minimum of 6 months with serial biopsies or autopsy studies. All these patients had transurethral resection of all possible tumor tissue 2 weeks before isotope injection. This provides good biopsy material and decreases the total weight of tumor tissue which must be injected. The two-week interval allows healing of the cut tumor surfaces and decreases isotope leakage at the time of injection.

These patients all had their tumors injected through regular suprapubic bladder incisions. Great care is taken to pack off and completely cover all tissue surfaces which are not to be actually injected with isotope. The inadvertent spillage of 0.1 ml. of solution could possibly result in 88,500 rep. of radiation to that spot. Severe tissue damage symptoms and of severe radiation ulceration may result from failure to maintain absolutely meticulous injection technique. The isotope solution should be treated with the same respect that a heavy culture of virulent tubercle bacilli would enjoy in the operating room or in the laboratory.

Based on our experience in the laboratory and in surgery, decontamination of the intact skin, metal or rubber gloved surfaces can be readily accomplished by vigorous scrubbing with soap and water while the contamination is still wet. However, if the chromic phosphate is allowed to dry on a surface, its removal is next to impossible without removing the surface on which it dried. The decontamination of ground glass syringes, cloth and tissue surfaces exposed by surgery is very difficult. Hence too much emphasis cannot be laid on the need for considerable caution in the handling and monitoring of radioactive chromic phosphate.

The very magnitude and complexity of the cancer problem make it worthwhile to offer only a few, short term clinical observations on these 25 patients, and brief comment on some of the technical problems encountered.

There were fourteen far advanced inoperable prostatic carcinomas and eleven similar recurrent bladder cancers. (See table 2.)

Generous transurethral biopsies of the isotope injected areas taken three to six months after injection in 10 patients suggested that the areas of tumor tissue had undergone marked cellular alteration. This would indicate that the dosage delivered by 100 microcuries of P^{32} per gram of tumor tissue is adequate to locally destroy some prostatic and bladder carcinomas.

Aside from locally altered tumor cells, these patients have all shown marked decrease in bladder symptoms. Contrary to the situation when 8,000 to 9,000 r. of radium or deep x-ray therapy given to the bladder results in severe discomfort, strangury and bladder contracture, all the isotope patients have had gratifying relief from pain, marked diminution or even cessation of hematuria and clots and decreased bladder spasms. Three of the bladder cancer patients (two now dead) came back voluntarily for repeat injection of their recurrent or incompletely injected tumors. All three did so because of temporary relief of symptoms after initial isotope injection. Even though patients have died of extensive cancers, both they and their families have expressed belief that there was symptomatic relief for varying lengths of time after injection before extravesical tumor brought them to autopsy.

None of the bladder or prostate cases showed any blood dyscrasias in careful pre- and post-injection studies. Serial blood and urine assays for radioactivity are run on these patients. Bone marrow studies have all been within normal limits throughout treatment. No appreciable isotope leakage or loss from the injection site has been observed with careful urine assay for 48 hours after injection.

Postoperative complications have been limited to 5 patients with slow closure of their suprapubic skin wounds. One man had a temporary suprapubic fistula of 5 weeks' duration. His case illustrates the clinical problems often faced. A previous hemicystectomy of the dome for carcinoma of the bladder was followed by multiple recurrences treated with three transurethral resections over four years. His first isotope injection was highly successful. Six months later a new tumor grew in the previously normal bladder dome scar. Following open isotope injection of this area of tumor and scar, his urethral catheter block resulted in suprapubic leakage. After learning to keep his urethral catheter open, suprapubic wound healing was solid in 3 days.

A most striking case of symptomatic relief was seen in a 46 year old man with an epidermoid carcinoma in a bladder diverticulum plus deep pelvic, abdominal and suprapubic tumor extension. His suprapubic wound was exquisitely tender to touch. He was unable to wear clothing on the area 6 months after his original surgical exploration. There was complete relief of pain within 48 hours after suprapubic isotope injection. This area was still nontender when he died 2 months later from widespread abdominal metastases.

No rectal complaints or difficulties have developed even though we have intentionally injected isotope right next to the rectal mucosa in several tumors. Some temporary diminution of bladder capacity occurred during the first 2 weeks, i.e., from a capacity of 450 cc down to 300 cc, but return to near normal capacity is the rule.

A second objective of the program along with clinical evaluation of dosage necessary to alter tumor cells, was the study of distribution patterns of the injected isotope. We are now convinced from careful autopsy study that this is perhaps the most important single factor in achieving the uniform destruction of larger tumors. With a radiation source whose penetration at maximum is

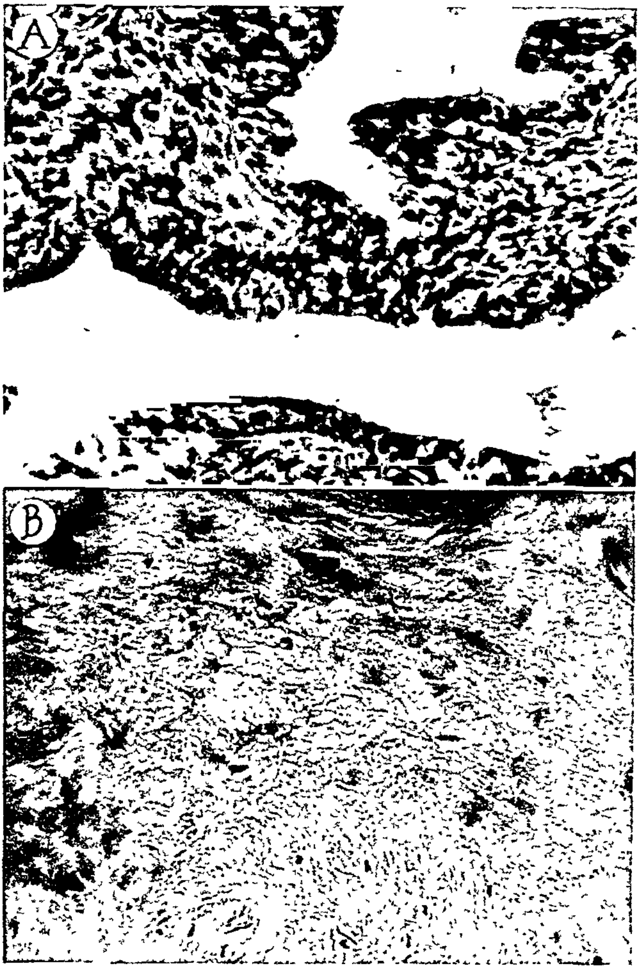

FIG. 1. *A*, L. J. H., No. 284403, aged 59, far advanced adenocarcinoma of prostate, group C. Transurethral biopsy of prostatic tissue. *B*, transurethral biopsy of prostatic carcinoma 3 months after injection of 6 millicuries of radioactive chromic phosphate. Urologically, patient completely asymptomatic. Prostate rectally feels like a small, irregular, fibrous gland.

only 8 mm. and whose average penetration is 3.2 mm., it is obvious that uniform, even distribution of isotope throughout the tumor is essential.

A striking illustration was the case of a 69 year old man with far advanced bladder carcinoma of 4 years' duration. His suprapubic tube had caused recurrent, severe bladder hemorrhages and bladder spasms. He was injected with isotope and discharged home 2 weeks later, already alleging symptomatic relief and showing no appreciable bladder bleeding. He died 2 months post-isotope injection from congestive failure. His bladder specimen showed deep areas of tumor necrosis and slough with solid viable tumor areas nearby. There was evidence of bowel adherence to the bladder dome tumor but no bowel necrosis. Manual injection of the isotope, while grossly easy, had failed to scatter the radioactive particles evenly through the tumor.

This problem is now under intensive study using a new electrically powered,

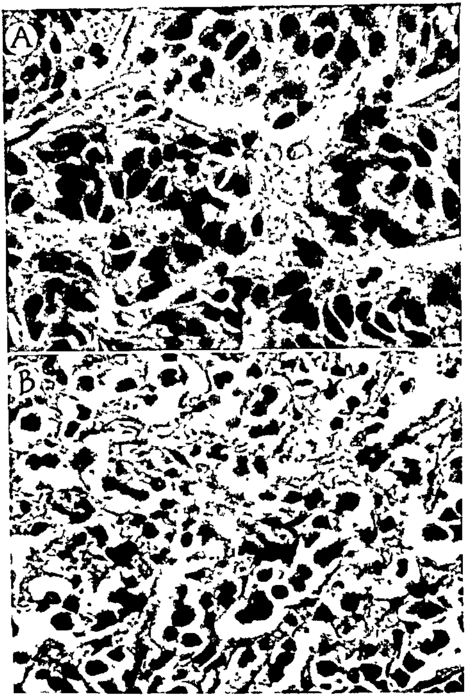

FIG 2. B. W. C, No. 278307, aged 62. Anaplastic carcinoma of bladder. January 1953, palliative bilateral ureterosigmoidostomies done. Bladder hemorrhage, spasm and slough continued. *A*, June 1953, biopsy of persistent anaplastic tumor with extravesical extension. Bladder tumor injected with 5 millicuries of radio-active chromic phosphate transvesically. Immediate postoperative relief of bladder discomfort. Patient has had continued mild hyperchloremic acidosis necessitating large amounts of soda bicarbonate orally daily, but has no bladder complaint. *B*, biopsy of previous bladder carcinoma 9 months after isotope injection. Grossly, no evidence of tumor on cystoscopy or bimanual palpation.

automatic isotope injector which allows the surgeon to devote all of his attention to the injection sites. The injector delivers a standard volume of isotope under uniform, reproducible pressure. This should permit more adequate distribution and therefore more complete tumor ablation.

The illustrated sections of tissue from pre- and post-injection bladders and prostates suggest some of the changes seen after interstitial irradiation with P^{32} (fig. 1). Much more insight is gained from whole serial section study but single fields highlight the most dramatic pathologic findings. By the use of tissue radio-autographs one can prove the localization of isotope in tissue and then study the sections with the autograph as a guide.

SUMMARY

It would appear from this group of 25 patients treated by manual, interstitial injection of radioactive chromic phosphate that a dose of 100 microcuries of P^{32} per gram of tumor will exert profound effects on tumor tissue. This amount of isotope per gram of tumor appears to be without serious systemic or local toxic effects and is well retained in tissue. Patients have noted prompt relief of bladder irritative symptoms even with fatal extravesical tumor extension. Better distribution of interstitially injected isotopes is now the fundamental problem to be solved.

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SARCOMA OF PROSTATE AND BLADDER

JAY LONGLEY

Because of the astounding effect of the antibiotics in infectious diseases, malignancy has become an increasingly important cause of death in children By 1949 it was the second most common cause, and a considerable number of the lethal tumors were in the urinary tract [1] Neoplasms are now exceeded only by leukemia as the major cause of death from malignant disease in the very young

The majority of these tumors in children were sarcomas, and the usual site was the kidney There have been several reports and reviews of renal sarcomas within the last ten years, but no comprehensive study has been made of these tumors involving other portions of the urinary tract, especially the prostate and bladder Hence this review seems timely

Thirty seven cases of sarcoma of the prostate and fifty seven of sarcoma of the bladder have been collected for study Twelve of these from the Mayo Clinic have not been previously reported We have limited our study of the literature to the last 20 years because the problem has been better understood during that period, more adequate staining methods have been available, and the majority of the authors have been accessible for additional information

SARCOMA OF THE PROSTATE

Review of literature The possibility that sarcoma might occur in the prostate gland was first suggested by Stafford[2] of London in 1839, when he reported such a case in a 5 year old boy The most recent summary of the literature was by Melicow[3] in 1943, who stated that about 200 cases had been published Since his report there have been 14 more in the English and four in the foreign journals

Classification The following classification has been used in this study

A Myosarcoma
  1 Rhabdomyosarcoma
  2 Leiomyosarcoma
B Spindle cell sarcoma
  1 Fibrosarcoma
  2 Spindle cell sarcoma
C Miscellaneous types
  1 Myxosarcoma, osteosarcoma, liposarcoma, neurogenic sarcoma, etc

Origin Embryologically, sarcoma of the prostate arises exclusively from the stroma This consists of the muscular and fibrous elements from the mesodermal tissue of the genital cord, containing the terminal portions of the wolffian and mullerian ducts, and from the circular musculature of the urogenital sinus By

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Read at annual meeting, Western Section of American Urological Association, Victoria, B C April 19 22 1954

Abridgment of thesis submitted by Dr Longley to the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Urology

[1] Cancer among children Statistical Bulletin, 30 1–4, January, 1949

[2] Stafford, R A Case of enlargement from melanoid tumor of the prostate gland in a child of 5 years of age Med Chir Tr 22 218 221, 1939

[3] Melicow, M M et al Sarcoma of the prostate gland J Urol , 46 675–707, 1943

analogy in the female the musculature of the uterus is also derived from the genital cord and may become the site of leiomyomatous or leiomyosarcomatous growth in adult life.

Age incidence. Prostatic sarcoma may occur at any age, though some types are more common at certain age levels. In the series I am reporting 20 cases (54 per cent) occurred during the first two decades of life and 81 per cent were found before the sixth decade. Obviously, therefore, sarcoma must be suspected in any greatly enlarged prostate occurring in a patient under 50 years of age. At the Mayo Clinic between the years 1940 and 1950, among 1500 patients with malignant prostatic disease, five were found to have sarcoma, an incidence of 0.3 per cent.

Rhabdomyosarcoma. About 23 cases of primary rhabdomyosarcoma have been reported. The average age at onset of symptoms was less than eight years and the average length of life after recognition was seven months. Metastases were present in all cases, local invasion and distant metastases with equal frequency. Symptomatically the patients all presented the usual symptoms of prostatism, with hematuria a common feature. The prostate on rectal palpation was usually soft and not tender. The tumor grossly involved one or all lobes and was usually large. The cut section was soft, pale, fleshy, and friable. Grape-like pedunculated portions were easily detached. Histologically the cells varied in size, with irregular, large, and multiple nuclei. A striking feature was the large number of giant cells, many of which showed the longitudinal and transverse striations peculiar to this tumor. Mitotic figures were seen throughout the sections and invasion of the blood vessels and the capsule was common.

Leiomyosarcoma. Approximately 17 cases of proven primary leiomyosarcoma of the prostate have been recorded. They are probably derived from the smooth muscle fibers within the interstitial framework and the capsule of the gland. Contiguous structures of smooth muscle origin, and hence potential sources of this tumor are the utricle, bladder, seminal vesicle, and rectum. Primary growths of any of these organs may be confused with primary prostatic sarcoma. Hence Young[4] suggested the use of the term "sarcoma of the prostate and adnexa" without attempting to differentiate the source except in small localized processes. The average age was 44 years, and the average duration of life from onset of symptoms was 3.5 years. One patient reported by Counseller[5] received x-ray and radium therapy and lived 17 5 years. The average survival of patients who received radiation was 5 years while the others lived on an average only 3 years.

The gross tumors were smooth, encapsulated, and friable, with less necrosis than in the former group, and as a rule the microscopic picture was less anaplastic. The basic histological difference between the two groups was the absence of striations in the tumor cells of the leiomyosarcoma group. Metastases to distant areas and extension to surrounding structures were present in the majority of these patients who came to autopsy.

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[4] Young, H. H.: Malignant tumors of the prostate. Am. J. Surg., 6: 667–678, 1929.

[5] Counseller, V. S. and Bedard, R. E.: Sarcoma of prostate gland. J. Urol., 43: 836–843, 1940.

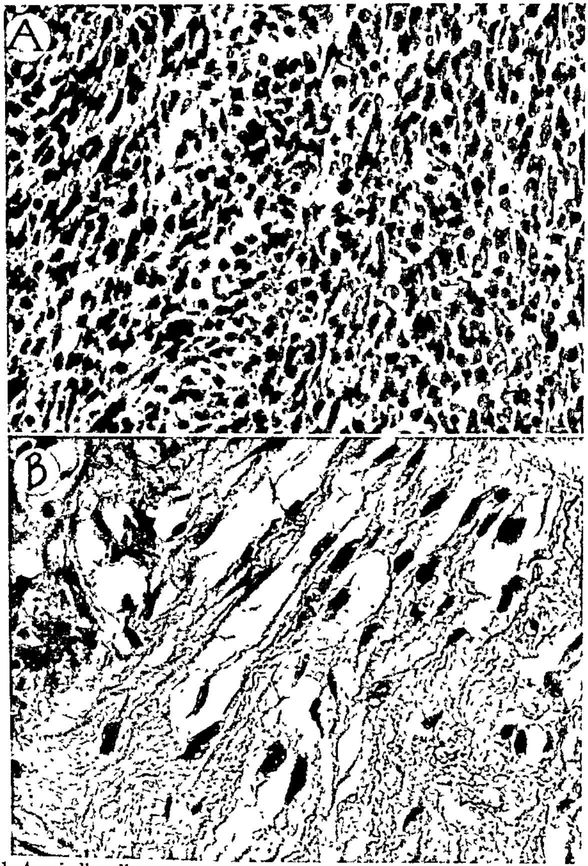

FIG. 1. *A*, spindle cell sarcoma of prostate (noncollagen producing). ×455 *B*, spindle cell sarcoma of prostate showing tapered cells with intercellular collagen. ×415.

Spindle cell sarcoma. Twenty-one cases of primary spindle cell sarcoma of the prostate have been reported. This 20-year study included eight from the literature and two new cases. The patients averaged 11 years of age. Their life expectancy was only 2.5 years and was not materially influenced by any type of surgical procedure. The symptoms were essentially the same as in the other types of sarcoma of the prostate and widespread metastases were the rule.

Pathologically, spindle cell sarcoma of the prostate resembles other connective tissue malignant tumors occurring in the breast, vulva, hand, etc. The cut section is white or gray-white, firm, and shining. Microscopically, the tumor is made up of elongated spindle-shaped cells with no consistent arrangement, but in small areas running in one direction or in whorls. There are frequent mitotic figures and the supporting stroma is not prominent because of the high degree of cellularity with predominating spindle-shaped cells. See figure 1.

Fibrosarcoma. We distinguish these from the previous spindle-cell group only because of the presence of large amounts of fibrous tissue in the specimens. There were too few cases to arrive at any conclusions.

Myxosarcoma. Only 2 cases were reviewed and the tumors consisted of spindle-shaped cells with hyperchromatic nuclei. Many mitotic figures were found and there was abundant blue-staining cytoplasm. No attempt was made to draw any conclusions from these few cases.

Total mortality in sarcoma of the prostate. The average length of survival of all the patients in this 20-year study of prostatic sarcoma was 21 months. This included all types, from the most malignant spindle-cell sarcoma, with a survival average of only 2.5 months, to the much less malignant leiomyosarcoma with an average duration of life of 3.5 years. This variation in life expectancy emphasizes the importance of precise histopathological diagnosis as a criterion of prognosis.

Treatment. Many forms of therapy have been used in attempting to prolong the lives of these patients. In most of them the tumor had already metastasized and only palliative procedures could be offered. Because of the rapid and extensive metastases none of these patients received radical prostatectomy and cystectomy, and it is doubtful if any additional benefit would have been demonstrated.

The leiomyosarcomas, which occurred in an older age group than the others, seemed to be radiosensitive.

SARCOMA OF THE BLADDER

Sarcoma is one of the rarest types of malignant tumor of the bladder, only 156 authentic cases having been recognized up to 1935.[6] Since that time 49 more have appeared in the literature and we are including six more, making a total of over 200 in all.

One of the first comprehensive studies of the subject was published in 1926 by Cecil[7] who classified the tumors as follows:

1.	Round cell	72 cases
2.	Spindle cell	17 cases
3.	Mixed cell	16 cases
4.	Fusiform cell	14 cases
5.	Fibro cell	14 cases
6.	Lympho cell	13 cases
7.	Alveolar cell	12 cases
8.	Myxo cell	11 cases
9.	Myo cell	9 cases
10.	Miscellaneous types	rare

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[6] Rabson, S. M.: Atypical carcinoma of the urinary bladder. J. Urol., **36**: 638–669, 1935.

[7] Cecil, H. L.: Sarcoma of the bladder. J. Urol., **16**: 471–495, 1926.

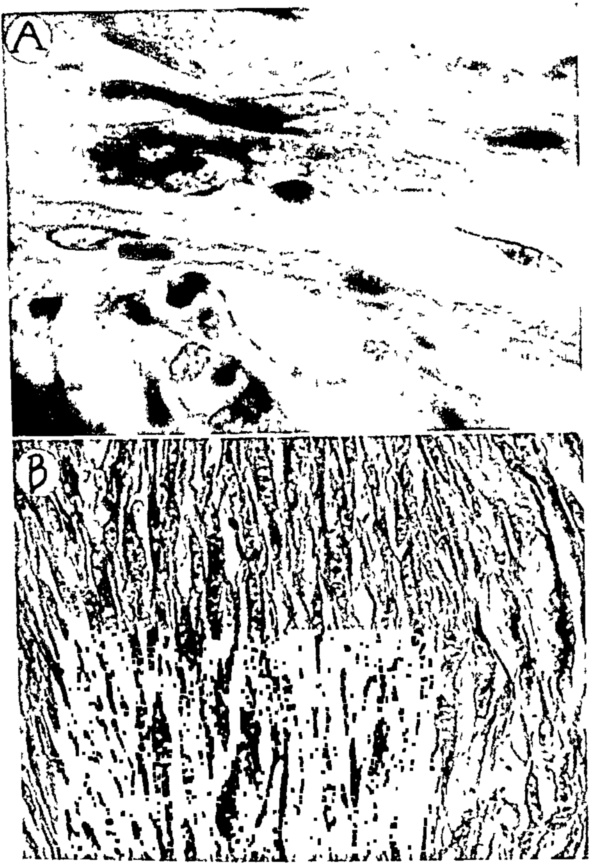

FIG. 2. *A*, rhabdomyosarcoma of bladder ×1200. *B*, leiomyosarcoma of bladder. ×390.

If one were to tabulate the frequency of the various types today the order would be almost reversed. Myosarcoma now exceeds all others, if lymphosarcoma is excluded, making up 58 per cent of the 56 cases reviewed. This reversal of frequency of types is probably due to more accurate study in recent years. Saphir[8] and McDonald[9] pointed out that the first diagnostic impression of a sarcoma will often be changed after complete study of the entire tumor. They pointed out that electrocoagulation of the surface of the tumor may destroy practically

[8] Saphir, O. and Vess, A.: Carcinosarcoma Am. J. Cancer, 33: 331–361, 1938

[9] McDonald, J R., et al.: Carcinoma of the urinary bladder imitating sarcoma. J. Urol., 46: 38–51, 1941.

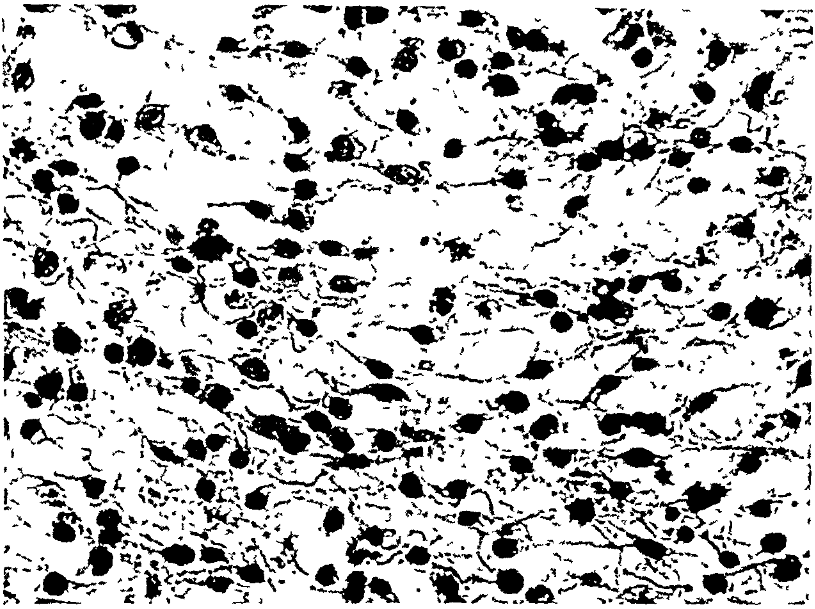

FIG. 3. Fibromyxosarcoma of bladder. ×435.

all of the papillary structure, leaving the sarcomatoid portions which are deeper within the bladder wall.

Origin. This is still controversial as no one theory explains the origin of all of these tumors. One has only to note the variety of locations in which they appear in the bladder to recognize that no area is immune, though the majority are found on the lateral wall, well removed from the sites of vestigial structures.

Frequency of occurrence. This has been recorded by various writers in the past. Price[10] reported 8 out of 55 bladder tumors; Samuel[11] found only 2 out of 522 vesical tumors at the Memorial Hospital prior to 1930. From 1942 to 1951 some 2300 new bladder tumors were seen and there was only one sarcoma.

Age of occurrence. Some 56 cases were included in this study. They occur both in the very young and the old, with a peak frequency below the age of 5 years. Specific cellular types appear most commonly in different age groups. The average age of the patients with leiomyosarcoma was 52 years, rhabdomyosarcoma 18 years, spindle cell 36 years, and fibromyosarcoma and myxosarcoma about 19 years. The same classification of the various types of sarcoma described in discussing the tumors of the prostate is applicable to sarcomas of the bladder.

Symptomatology. The majority of the patients, 52 per cent, noticed painless hematuria as the initial symptom. About one-third complained of dysuria and obstructive symptoms. It is interesting that hematuria was a rather rare initial finding in children.

Mortality. Of the entire group of 56 patients, 10 were still alive when the review was completed in 1952, and one reported by Feggetter[12] had survived for 15 years. Of the patients dead of the disease, the average duration of life after the onset of symptoms was less than one year. Only one patient with rhabdomyosarcoma had survived, and the average duration of life in that group was 6.6 months. On the other hand, the average life of the patients with leiomyosarcoma was 19 months.

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[10] Price, L. W.: Sarcoma of the urinary bladder. Glasgow M. J., **137:** 23–29, 1941–1942.

[11] Samuel, E.: Radiological features of vesical leiomyoma and leiomyosarcoma. Brit. J. Radiol., **20:** 423–425, 1947.

[12] Feggetter, G. Y.: Sarcoma of the bladder. Brit. J. Surg., **25:** 382–387, 1937.

Pathology. Grossly the tumors vary from filamentous and polypoid shape to the rare crater-formed types. Those composed primarily of muscle tissue are pedunculated, friable, and botryoid, while the connective tissue tumors are firm, nonpedunculated, and sometimes sessile. The former are much more highly vascular, friable, and bleed more easily. All types appear to be encapsulated as a rule. Microscopically they differ little from the findings described previously in sarcomas of the prostate. There appears to be some tendency to myxomatous changes in bladder sarcomas, but the general cellular structure remains similar. The capsule is usually a single layer of flattened cells. See figures 2 and 3.

Metastases occurred as a rule first by direct extension and secondarily by the blood stream. Distant metastases to the lungs, bones, kidneys, adrenals, and more rarely to the peri-aortic lymph nodes, have been described.

Therapy. The treatment of sarcomas of the bladder so far has not differed from that employed for epithelial tumors. They are highly malignant, and segmental resection and/or cystectomy, with or without radiation, have been the most successful procedures and appear to have provided the longest survivals of the group. As in prostatic sarcoma the rhabdomyosarcoma seems to be more malignant and difficult to treat. It does not respond to radiation as well as the leiomyosarcoma.

SUMMARY

A study of sarcoma of the prostate and bladder includes 94 cases found in the literature of the last 20 years or here reported (12 cases).

Sarcoma of the prostate occurs at two age periods, the majority of patients being under the age of 20 years.

Rhabdomyosarcoma and spindle cell sarcoma of the prostate are rapidly fatal, while leiomyosarcoma has a somewhat more favorable prognosis.

The prognosis is generally better in the older patients, regardless of the type of sarcoma.

Leiomyosarcoma seems more radiosensitive than the other types, where radical surgery offers the only hope, though the results so far have been disappointing.

Bladder sarcomas also appear at two age periods, under 5 or over 50 years of age.

Anaplastic transitional cell carcinoma of the bladder may be confused with sarcoma unless precise histological study of the specimen is done.

Rhabdomyosarcoma and leiomyosarcoma are the most common forms of sarcoma in the bladder. Their clinical course and characteristics and their pathological patterns are similar to comparable lesions of the prostate.

Corona del Mar, Calif.

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A TRUE HERMAPHRODITE

G. W. SCHWIEBINGER AND C. V. HODGES

From the Division of Urology, University of Oregon Medical School, Portland, Ore.

The problems of the intersex have always intrigued the lay imagination, and are no less of an enigma to the medical profession. Earlier diagnosis, through awareness, could in many instances abort or modify the psychological trauma and the hormonal imbalances that occur in the adult hermaphrodite. The main types of hermaphroditism are the male pseudohermaphrodite, the female pseudohermaphrodite, and the true hermaphrodite. It is the latter with which we are here concerned.

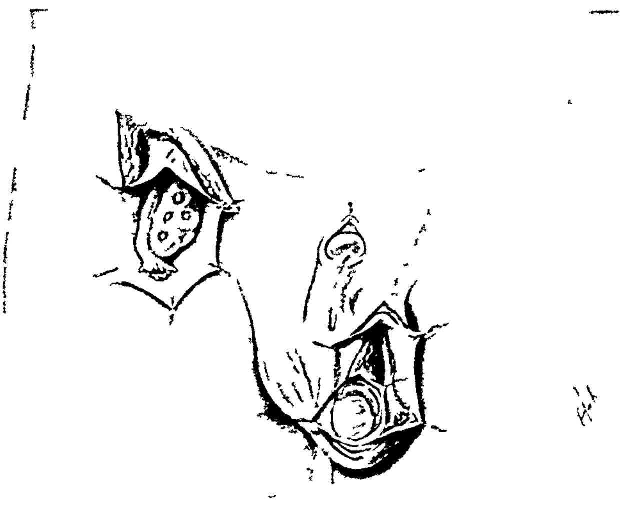

FIG. 1. Operative findings: testis, epididymis, vas deferens, and fallopian tube in left scrotum; right ovary with fallopian tube after delivery from intra-abdominal position

The true hermaphrodite is an individual who possesses both ovarian and testicular tissue. Ordinarily this must be confirmed by histologic examination. Using Hinman's classification of true hermaphroditism for simplicity, they may be divided into: bilateral, with a testis and ovary on either side, either separate or united (ovotestis); unilateral, with testis and ovary, either separate or united, on one side, with either testis or ovary on the other; and lateral or alternating, with testis on one side, ovary on the other. In 1937 Young compiled a list of 21 acceptable cases from the literature. McIver, Seabaugh and Mangels in 1944 brought the literature up to date summarizing 11 additional cases and reporting two cases of their own. Fischer, Lischer, and Byars in 1952 found 14 subsequent cases and added one of their own. Since then five more cases have appeared in the literature. The case we are about to report is the fifty-fifth. It is the sixteenth of the lateral or alternating variety.

Read at annual meeting, Western Section of American Urological Association, Victoria B. C. April 19–22, 1954.

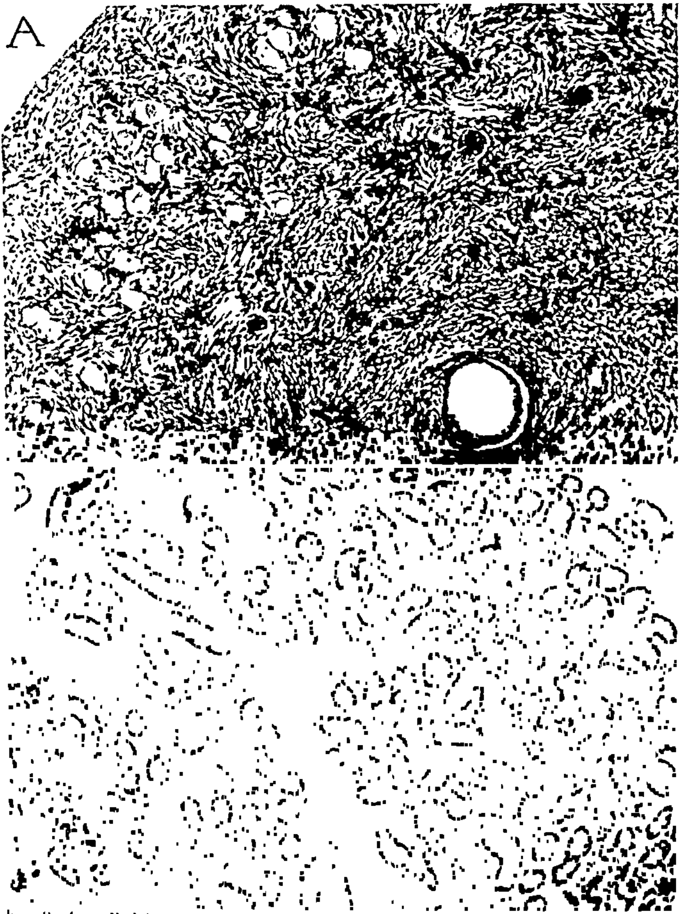

Fig. 2 *A*, well differentiated right ovary with numerous primordial follicles and one graafian follicle. *B*, biopsy from left testis showing immature seminiferous tubules.

CASE REPORT

The patient was first seen at the age of 5 because of penoscrotal hypospadias and right cryptorchidism. Physical examination described a normal appearing young male. A moderate amount of chordee and a penoscrotal hypospadias were present. The left testis was in the scrotum and appeared normal to palpation. The right testis could not be palpated in the scrotum or in the inguinal canal. It was elected to correct the hypospadias first. A first stage repair was performed.

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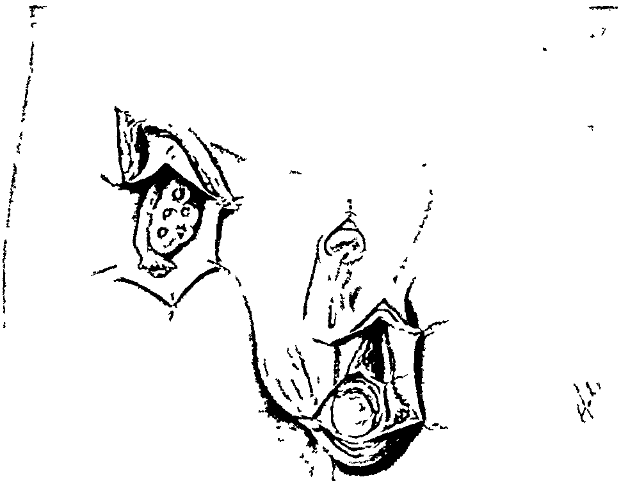

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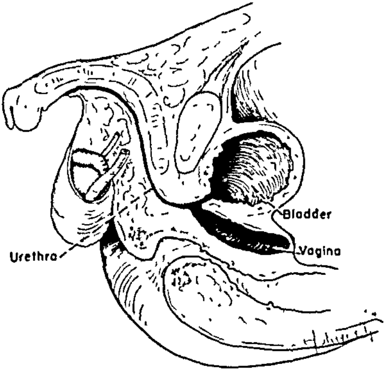

FIG. 4. *A*, semi-diagrammatic sagittal section showing vagina arising from posterior urethra.

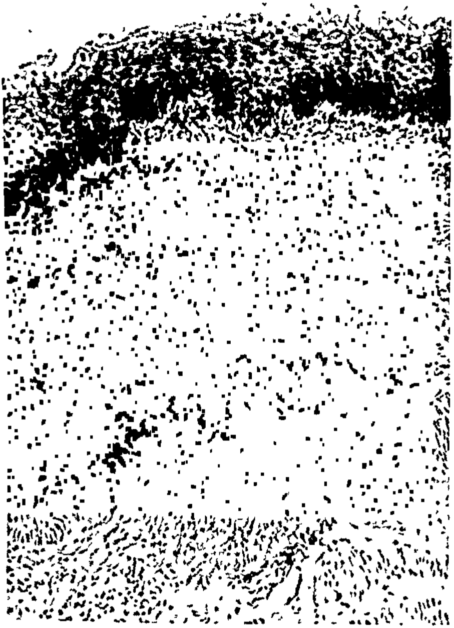

FIG. 5 Infantile vagina

present, a normal, cystic-appearing ovary and fallopian tube with fimbriated end presented. Incision into the scrotum was then performed. A normal appearing testis with a fibrotic epididymis and vas deferens was found along with another fallopian tube with a fimbriated end (fig. 1). Laparotomy revealed only a pseudo-pouch of Douglas formed by two peritoneal folds; no other female structures were found. Frozen section confirmed the gross impressions about each gonad. A right salpingo-oophorectomy and herniorrhaphy were performed, as well as a left salpingectomy. Paraffin sections of the surgical specimens revealed an immature testis, normal fallopian tubes, and a well differentiated ovary (figs. 2 and 3). Cystoscopy performed during the patient's convalescence revealed the absence of the verumontanum and prostate, but a vaginal orifice opening into the area where the utricle would normally be expected was found (fig. 4). Three months later, colpectomy was performed (fig. 5).

DISCUSSION

Historically, Young found that the origin of hermaphroditism was traced to a celestial union of Aphrodite and Hermes who brought forth a child endowed with the attributes of both father and mother. They therefore gave it both parents' names and we had Hermaphroditos. The etiology of this condition remains a mystery. It is felt that this represents a hormonal disturbance in the developing embryo, most likely at the 13–15 mm. stage when gonadal differentiation takes place. Cawaditas on the other hand feels that this form of intersexuality as an entity is nonexistent. He states that in nearly all cases of true hermaphroditism one or the other of the gonadal structures is rudimentary and that further, all men show female glandular cells and all women have rudimentary testicular tissue. It is not the purpose of this paper to settle this argument. The clinical diagnosis may only be made definitely by histological evidence of the co-existence of ovarian and testicular tissue. No particular constitutional type or body build seems to be consistently associated with this disease. Psychological problems seem to be primarily related to the genital abnormalities rather than any hormonal imbalance. A hypospadiac phallus is a common finding, although normal external genitalia do occur. A uterus, fallopian tubes, and a vaginal opening into the urethra are frequently described. As one or more of the gonads are usually found intra-abdominally, the external genitalia may resemble either the female labia or the male scrotum with cryptorchidism. Inguinal hernias are frequently found. Laboratory studies of the androgen and estrogen excretion have so far revealed no significant abnormalities. However, 17-keterosteroid excretion studies should, nevertheless, be done, as should x-rays of the skeleton for bone age. As the pragmatic sex is obviously somewhat difficult to determine, especially in the youth, treatment is directed towards development of the genetic sex. This necessitates exact diagnosis by examination of both gonads microscopically, laparotomy to determine presence or absence of accessory reproductive organs, and cystoscopy to evaluate that portion of the genital tract. Ideally these procedures should all be carried out prior to extirpation of either gonad and the situation discussed with the parents. If, however, the condition was suspected prior to operation, more efficient management would result On reviewing the anatomical findings of the previously reported cases we have been impressed with the frequency of hypospadias and cryptorchidism The findings in our case stimulated this review As a result of these findings it would not seem illogical to recommend urethrocystoscopy in all cases where this unusual combination exists, and to anticipate to a degree this problem when cryptorchid repair is done By preparing the parents in advance that abnormalities of this type do occur in the cryptorchid gonad, laparotomy may then be performed if indicated, the entire story unfolded, and appropriate surgical therapy instituted at a single session

SUMMARY

The fifty-fifth case of true hermaphroditism is presented

A brief discussion of hermaphroditism is included

It is suggested that when the combination of hypospadias and cryptorchidism is found, true hermaphroditism may be suspected and further diagnostic procedures are indicated

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PAPANICOLAOU EXAMINATION OF URINE IN DIAGNOSIS OF URINARY CANCER. I. AS A TEST IN MASS SCREENING

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This paper constitutes the first portion of a report covering an evaluation of the use of the Papanicolaou staining method to examine the urine in an effort to diagnose cancer of the urinary tract. The project is divided into three parts:

1) Papanicolaou technique in mass screening.
2) False positive results in the diagnosis of renal carcinoma.
3) Use in follow-up care of patients after treatment for bladder tumors.

Despite continued progress in the treatment of cancer by means of radical operation, deep x-ray, radium and radioactive isotopes, early diagnosis remains the most important single factor in the control of cancer.

The problem in Urology, as in all fields of medicine, is to initiate reasonable therapeutic procedures sufficiently early to afford hope for cure. If a simple, inexpensive test to detect early cancer could be developed, as the minifilm is applied to mass screening for pulmonary tuberculosis and other thoracic lesions, a powerful weapon would be available. In theory, the Papanicolaou technique seems ideal; it is being applied widely to detect cancer of various organs, achieving particular significance in the early stages of uterine cancer.

In assessing the efficacy of Papanicolaou examination of the urine in detecting cancer of the urinary tract by mass screening, smears were made of material from 1,575 persons.* Candidates for the survey were selected at random from in- and out-patients at Stanford University Hospitals and others who consented to participate. Most patients did not complain of any symptoms of diseases of the urinary tract. The purpose of the study was to detect cancer before hematuria or other symptoms developed—to make the diagnosis during the incipient period between the first cell mutation and the first clinical symptom. Obviously diagnosis made in this stage permits the most effective treatment.

The technique employed was developed from procedures described by Papanicolaou, Harrison, Daut and other pioneers in the field. Smears were made from freshly voided urine, as cellular elements disintegrate rapidly at a rate directly proportional to the time interval between collection and preparation. Four hours was set as the upper limit of suitability. Voided urine from both sexes was examined. Although urine voided by males is satisfactory, it is better to catheterize females to eliminate the possibility of vaginal contamination. However, catheterization was not considered practical for mass screening.

Approximately 100 ml. of urine from each subject was centrifuged at 2,000 revolutions per minute for 10 minutes. The sediment was spread on two slides prepared with a thin film of albumin as an adhesive agent. When the sediment

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Supported by a State of California Department of Public Health Grant.

* Expenditures for this survey totalled approximately $4,000, about $2.54 per individual tested.

✓

TABLE 1. *Grading smears*

I. Negative	Normal transitional cells
II. Doubtful	Slightly atypical cells—repeat in 3 months
III. Doubtful	Atypical cells suspicious of malignancy—repeat immediately
IV. Positive	Atypical cells suggestive of malignancy
V. Positive	Atypical cells highly suggestive of malignancy
Unsatisfactory	Fewer than 6 cells per slide

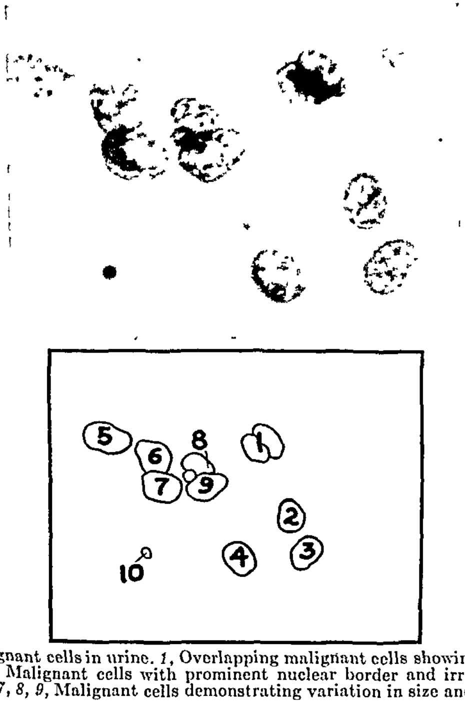

FIG. 1. Malignant cells in urine. *1*, Overlapping malignant cells showing indistinct cyto plasm. *2*, *3*, *4*, Malignant cells with prominent nuclear border and irregular chromatin patterns. *5*, *6*, *7*, *8*, *9*, Malignant cells demonstrating variation in size and shape of nuclei. *10*, Lymphocyte.

had partially dried, each slide was immersed in a fixative of ether and 95 per cent alcohol in equal parts. Slides were immersed for from 10 minutes to 48 hours before staining by the original Papanicolaou technique. Preliminary screening was carried out by cytology technicians. All questionable and suspicious slides were then studied by staff members with wide experience in Papanicolaou studies.* Smears were graded as indicated in table 1.

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* The authors express their indebtedness to Dr. Harold Lyons of the Department of Obstetrics and Gynecology and Dr. Donald Bittner of the Department of Pathology, Stanford University School of Medicine, for executing this part of the project.

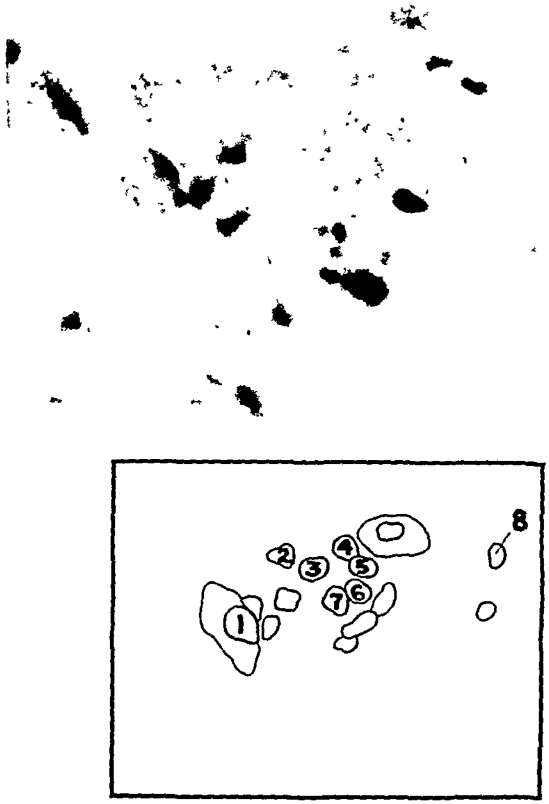

FIG. 2. Cells of doubtful malignancy. *1*, Large doubtful (III) cell with sharp nuclear border and hyperchromatic nucleus. *2, 3, 4, 5, 6, 7*, Cluster of six atypical transitional cells with indistinct cytoplasm. *8*, Round transitional epithelial cell with sharp cytoplasmic border.

In this system of grading groups IV and V suggest malignancy, V being more highly suggestive. However, neither is absolutely diagnostic of malignancy. In making our reports, we always stressed that biopsy of tissue is necessary for final confirmation.

One difficulty in interpretation was to distinguish some transitional epithelial cells from malignant cells, since the former varied considerably in structure. (Characteristic malignant cells are shown in figure 1. These have large hyperchromatic nuclei, varying in size and shape. The ratio of the nuclear size to cell size is markedly increased. The chromatin of the nucleus is located at the periphery and in clumps within the nucleus. The cytoplasm is indistinct. Malignant cells are frequently found in clumps.) Figure 2 is a photomicrograph of a doubtful smear with atypical cells considered suspicious of malignancy. The results of a repeat study of this urine were negative.

Of the 1,575 individuals examined in this study, 1,182 (75 per cent) yielded negative smears, 39 (2.5 per cent) were doubtful and 350 (22.2 per cent) were unsatisfactory. Smears were considered unsatisfactory when there was too little sediment, less than six cells, to permit intelligent interpretation. This proved to be one of the practical limitations of the test.

We had no means of ascertaining how many of the smears were negative al-

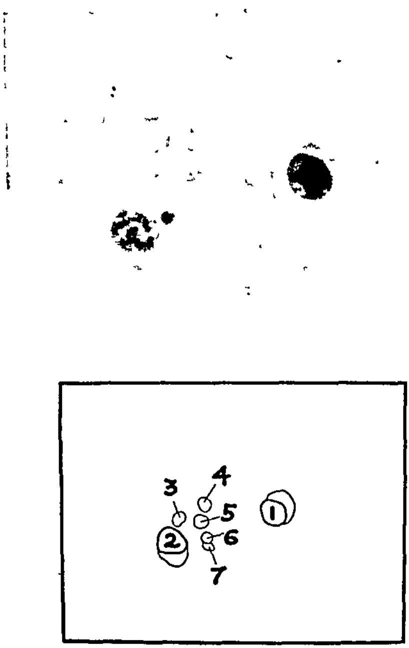

FIG. 3 False positive smear. *1*, Large hyperchromatic nucleus with sharp nuclear border and irregular chromatin pattern. *2*, Large nucleus with distinct border and irregular chromatin pattern graded as doubtful. *3*, *4*, *5*, *6*, *7*, Red blood cells.

though a tumor was present (false negatives). Obviously it would have been impractical to submit all persons to a complete urologic investigation in this type of survey. Approximately half of the subjects whose smears yielded doubtful results were retested. In each instance the results were negative.

In the entire series the smears were positive in only 5 patients (0.3 per cent). Two (both with findings placed in group V) were females later found to have carcinoma of the cervix, and two others (results in one, group IV and in the other, group V), a male and a female respectively, did not show evidence of tumor despite a most searching examination, including cystoscopy and retrograde pyelograms. The latter two are presumably free of urinary cancer, but we are keeping them under continued observation (fig. 3). The fifth subject (group IV) was found to have carcinoma of the prostate (table 2).

We did not discover one certain tumor of the urinary tract in screening 1,575 subjects. This makes it seem doubtful that the Papanicolaou examination of the urine is applicable to mass screening in an effort to diagnose malignancy early in this system.

Several factors mitigate against the application of the test to mass screening. First are technical disadvantages inherent in the method: a) In examining urine

TABLE 2. *Results in 1576 patients*

	No.	%
Negative I	1182	75.0
Doubtful II and III	39	2.5
Positive IV and V	5	0.3
Unsatisfactory	350	22.2

an extremely high proportion of smears were unsatisfactory because the amount of sediment was insufficient; in our series, 22 per cent, or one out of every five individuals tested. We have had no experience with the recently devised technique of centrifuging the urine with an adhesive agent such as serum; this technique might reduce this percentage. b) Another technical hindrance is the necessity of using freshly voided urine to avoid cell disintegration. This requires that the patient report to the laboratory in person at the time a technician is available.

Secondly, it is difficult to interpret the results. The services of a highly skilled cytologist are essential. This requires experience above and beyond the training of a general pathologist. Furthermore, even in most skilled hands, the percentage of false negative and false positive errors in interpretation is high, as we shall demonstrate in subsequent reports.

Thirdly, use of the test is limited because of certain pathologic characteristics of tumors of the urinary tract. Since the common type of renal carcinoma, that of the parenchyma, does not invade the renal pelvis in the early stages, malignant cells do not desquamate until late—usually after the occurrence of gross hematuria. On the other hand, tumors of the renal pelvis and ureter, well suited to detection by Papanicolaou examination, are extremely rare. Some tumors (e.g., papillomas) desquamate cells which are similar to normal transitional cells and frequently will not be identified for this reason.

We have reached the conclusion, therefore, that while Papanicolaou studies serve a useful purpose in the diagnosis of some forms of malignancy, the test in its present form is not suitable for mass screening of urine to detect cancer of the urinary tract.

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A NEW PROSTATIC LOBE FORCEPS

EDWARD WILLIAM WHITE AND FRANCIS OSLAY

The new prostatic lobe forceps (fig 1) is the result of considerable though trial and error covering over twenty-five years in prostatic surgery

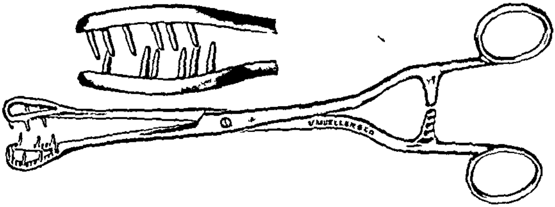

FIG 1

The new instrument is made of chrome stainless steel, case hardened It is considerably heavier than former prostatic forceps and is constructed to withsta heavy use when necessary The instrument is approximately 9⅜ inches lon the ringlets have been greatly enlarged and the most important change is t retrograde arrangement of all the teeth

An additional improvement, we believe, is a generous increase in the length the teeth within the forceps' grasp When the prostatic lobe is firmly within t grasp of the forceps, it becomes relatively easy to enucleate, especially within t deeper recesses of the prostatic capsule and posterior urethra, thus greatly simplifying prostatectomy

The authors are greatly indebted to V Mueller & Co of Chicago for c operative assistance in making this instrument possible

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Accepted for publication July 7, 1954

approaching the medulla, they become small, crenated, degenerated, and are removed by macrophages and microphages. This life cycle of the human adrenal cortex cell has been estimated. Roughly, it would appear that the cells producing the hormones for electrolytic, water balance and blood pressure are the youngest and most quickly formed, since they are essential for life preservation. The other hormones of less necessity for life are apparently produced more slowly.

The adrenocortical hormones have a chemical configuration like that of cholesterol. It has been reported that over 30 different related steroids have been isolated from animal adrenal glands. Of these, the actions of only a few are known, and those of interest are as follows.

1) 11-desoxycorticosterone, the acetate of which, known as DOCA, has been synthesized commercially; this acts almost exclusively upon sodium, potassium, chlorides, and water.

2) Corticosterone (compound B).

3) 17-hydroxy-11-dehydrocorticosterone, or cortisone. The latter two in various manners have relatively little action upon water and electrolyte metabolism, but have a profound influence on the sugar, fat and protein metabolism. Other steroids of close relationship also have sugar, fat and protein action, apparently characterized by the effect of oxygen on the eleventh carbon atom.

4) Androgenic action, albeit rather feeble (nitrogen, or protein anabolic or testoid hormone): a. adrenosterone, b. androsterone, c. dihydroandrosterone, d. 17-hydroxyprogesterone.

5) Estrogenic action: a. estrone, b. estradiol, c. estriol, d. progesterone.

The physiological actions of the hormones may be considered under the various headings of a) electrolyte and water metabolism (Na K hormones); b) sugar, fat and nitrogen metabolism (SFN hormones); c) dermographic and androgenic effects. The three actions combined unite to maintain the life balance and the various levels of physical and mental work capacities.

THE ELECTROLYTE AND WATER BALANCE

The electrolyte and water balance, under the 11-desoxycorticosteroids, maintain that balance by the effect of the hormones upon three areas—renal tubules, sweat glands, and salivary glands. It has been shown that when the concentration of these Na K hormones increases, the tubular re-absorption of the glomerular filtrate sodium tends to increase, while that of potassium tends to decrease. Thus, an increase of this Na K hormone will give a decrease in urine sodium excretion, thereby creating a serum sodium concentration, and will increase the urine potassium excretion with a serum potassium loss. With a decrease of this Na K hormone, the reverse would occur, with a sodium loss and a potassium retention. The sodium loss resulting from a decrease in Na K hormones causes a relative water loss and body dehydration. According to studies, similar effects are produced on both sweat and saliva. Secretory changes in sweat and saliva have less effect on the organism than do changes in the renal tubular activity, but the results of sweat changes are not negligible. An excess of the Na K hormones gives a positive sodium and a negative potassium balance. This, with an elevated serum sodium, should give an expansion of extracellular fluid with resulting edema and hypertension. The negative potassium balance tends to produce an intracellular potassium depletion. Excess sodium also has a tendency to involve bone cells, with displacement of other electrolytes.

With intracellular potassium deficiency, muscular weakness or paralysis may develop. Changes in skeletal and in cardiac muscle may occur, and in addition, marked alterations of the renal parenchyma may follow. Large toxic doses of the Na K hormones cause, in dogs, conditions which resemble diabetes insipidus.

With Na K hormone deficiency, the reverse occurs. Sodium and chloride *are lost in abnormal amounts and potassium is retained.* There is a shrinkage of extracellular fluid volume and extracellular dehydration. Circulatory failure may occur, with impairment of renal function. The subject becomes exceptionally vulnerable to salt and water deprivation.

With acute deficiency in cases under stress, the effects may be exceedingly rapid, as seen in the deficiency crises which may occur in Addison's disease. Excess hormone-secreting tumors of the adrenal, with resultant corticoid symptoms have, upon removal of the tumor, caused depletion and death, often within 24 hours. The conclusion must be that the amount of hormones readily available is usually small, or that apparently hormones are not stored in appreciable amounts. Also, the depletion ratio can not be easily offset by substitution with additional hormone; therefore, unless the hormone is given early and in large doses, it may not be effective. In other words, metabolically, the loss in hormone is more rapid than its restoration. The normal hypothalmic-pituitary adrenocorticotrophic hormone mechanisms necessary for stress are, to a considerable degree, dependent upon the Na K hormone production.

SUGAR, FAT, NITROGEN HORMONES (11-17 OXYCORTICOSTEROIDS)

The hormones active in these varied metabolic affairs are thought to accelerate the action of the formation of glucose and its transition into glycogen and perhaps its storage in the liver. Apparently it may work with insulin, increasing the utilization of circulating glucose, whereas epinephrine accelerates the changing of the hepatic glycogen into blood glucose. In the absence of SFN hormones, the body loses its capacity to mobilize fat. In the presence of an excess, it increases the rate of utilization of ketone bodies. SFN hormones accelerate amino acid breakdown. They produce changes in the lymphoid structures, and in the circulating eosinophils which undergo involution or lysis. Through their effect on the lymphoid structures, they may also produce a reduction of resistance to infection, thus making species susceptible to bacteria or higher forms of parasites to which they were formerly resistant. Recently it has been shown that host resistance against foreign cells or tissues may be destroyed by the SFN hormones.

An excess of SFN hormones inhibits fibroblastic proliferation and may produce a transitory reticulocytosis and a relative erythrocytosis. The inhibition of fibroblastic proliferation is most apparent upon the re-operative procedures in active corticoid excess patients.

Among other effects of these hormones has been the lessening of muscle fatigue. Also, in some fashion, these SFN hormones at times negate the action of the Na

K hormones upon electrolyte metabolism, so that even cortisone may not correct a water loss in a case of deficiency, and the patient may require a larger dose of DOCA.

The SFN hormones may increase certain renal functions. They may cause some alteration of brain metabolism. They also cause alteration in antigen antibody reactions as well as the changes in resistance to bacteria and to higher organisms.

Deficiency of these Na K and SFN hormones may occur through disease, trauma, or operative removal of the adrenals. Deficiency may also occur through disease, trauma, or removal of the pituitary, in which the adrenocorticotrophic hormone from the anterior pituitary is produced in deficient amounts or not at all. Excess of these hormones may be caused by the excess production of ACTH due to pituitary change, with subsequent hyperplasia or hypertrophy of the adrenals, or by independent tumor of the adrenal.

ADRENOCORTICAL ANDROGENS

The adrenocortical androgens appear to be produced in significant amounts at about the tenth to twelfth years of life. These hormones have a very weak androgen effect, usually only upon hair growth and distribution and on the skin changes usually seen with acne. Ordinarily they have no other sex effect. Deficiency of these hormones would most likely have little recognizable effect. Excess of the hormones, or as is most often the case, an alteration of the androgen as seen in adrenogenital virilism, frequently produces a marked effect. This has been seen in adrenogenital virilism with bilateral adrenal hypertrophy, or with adrenal tumor itself. The production of adrenal androgens is determined largely by the anterior pituitary through its adrenocorticotrophic hormone (ACTH). Since the production of ACTH is determined largely by the amount of cortisone in the circulating blood, the production of excess androgens may be decreased in bilateral adrenal hypertrophy by the administration of cortisone. With tumor, no such control is present, as the tumor has secreting cells which are apparently independent of control.

Na K and SFN hormones secreted in excess of requirement by the independent cells of an adrenal tumor produce effects of inactivity upon the ACTH cells of the pituitary and inactivity of all other normal adrenal cells. Removal of these excess-producing cells may be followed by acute addisonian crisis and death unless replacement therapy is administered until the pituitary and adrenals are able, by cellular regeneration, to re-establish control.

THE ADRENAL MEDULLA

Two closely related substances, epinephrine and nor-epinephrine, have been isolated from the adrenal medulla and are also secreted by the pheochrome cells of the sympathetic ganglia. Roughly 90 per cent of the normal is epinephrine and 10 per cent is norepinephrine. The effect of these two substances has to do with the production by the nerve endings of two additional substances, sympathin E and sympathin I.

The production of epinephrine and norepinephrine is apparently stimulated by the acetylcholine of the preganglionic nerve endings. Many factors prompt an immediate outpouring of medullary hormones; pain, hunger, rage, fear and hyperactivity being the most frequent. Drugs, such as histamine, may provoke the secretion. These catechols are secreted in the urine. In normals the excess in the urine appears to be norepinephrine and the minor secretion epinephrine, the reverse of the blood contents.

The effects of these catechols are different. Epinephrine produces a rise in blood pressure by increasing the cardiac output, with a fall of over-all peripheral resistance because of a vasodilation of the vascular bed of the muscles which outweighs the vascular constriction of the skin, mucous membranes, and the splanchnic area. There is an increase in the heart rate. There is an elevation of the glycogenolytic rate and of the basal metabolism. With norepinephrine, in contrast, there is little change in cardiac output, but there is a significant rise in over-all peripheral resistance. There is little effect upon the pulse rate, the glycogenolytic rate or the basal metabolism. The administration of both catechols at the same time sets up an antagonistic reaction between the two rather than having the modifying effect which one would expect. The vasoconstrictor action of norepinephrine is either nullified or over-balanced by the all-over vasodilation of epinephrine. Epinephrine in excess produces headache, palpitation and sweating, whereas norepinephrine excess may produce hypertension without the patient's being aware of his increased blood pressure.

Deficiency in secretion of these catechols is, at present, unknown in symptomatic disease. Excess occurs with tumor in pheochromocytoma. Three classes of symptoms may be seen in conjunction with excess secretion: silent, paroxysmal or continuous hypertension. Studies of all types of cases show that in all, the high levels of catechols are constantly present in the urine and in the blood. The amounts vary, and often have no relation to the symptoms. It is possible that tumor may produce some alteration in the catechols themselves or produce an antagonist, so that at times, large amounts are changed into active catechols, or the antagonist is nullified at times of attacks. Certain drugs may precipitate the attacks and others apparently control the effect of the catechols. Long, severe excitation, such as anesthesia, may produce a shock syndrome in cases of pheochromocytoma, and recovery may be expected only if the tumor is removed.

The continuous effect of these catechols apparently has some influence upon the maintenance of high circulatory balance, because when a tumor is removed, the blood pressure often falls to alarmingly low levels. The available circulating hormone appears to be exhausted rapidly, and for maintenance of a satisfactory pressure, a continuous norepinephrine drip is required. The recovery of the balance of secreting catechols of the body from the remaining pheochrome tissue is usually adjusted in 24 hours or so. During the period of administration of norepinephrine, there is a well-marked chilling of the extremities which disappears with the recovery of the patient's own catechol balance.

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PHYSIOLOGY OF KIDNEY

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Renal function, of which the mind of man began the intelligent study when Malpighi called attention to glomeruli in the seventeeth century, has become an increasingly complex metabolic and mechanical or physical mechanism. Its complexity is now rivaling that of the liver, and insofar as comparative size is concerned, has exceeded it.

The physical mechanism, a double walled filtration and osmotic membrane, the glomerulus and the rich vascular sheathing of the layers of renal tubular cells ingeniously function in a manner which we now duplicate to varying degrees by the many types of so-called "artificial" kidney. Kolff looks forward with some hope of artifically carrying out renal function satisfactorily enough to sustain life for long periods of time. Renal function resolves itself into a mechanism of filtration and re-absorption of numerous chemicals in aqueous solution, plus the elaboration of many recognized and yet unidentified chemicals. Primarily the rate of filtration is influenced by the pressure (osmotic and hydrostatic) and the blood flow through the glomeruli. Twenty-five per cent of the cardiac output goes through the kidneys with a full, open vascular bed. Vasomotor factors control the glomerulus pressure which, under average function conditions, result in a blood pressure of 20 mm. mercury. This plus twenty is a result of a positive cardiac produced pressure of fifty-five with the negative osmotic pressure due to plasma protein of twenty-five and a negative tissue pressure of ten. The tubular portions of the nephrons, of which there are approximately one million in each kidney, then modify the filtrate by excretion and re-absorption. The end product is the urine. Tubular function is carried on by a most complex chemical reaction series aside from physical factors. This chemical mechanism involves the endocrines, vitamins, enzymes, amino acids and so forth. During a period of 24 hours, 50 gallons of water, ½ pound of glucose and 2½ pounds of salt are filtered through the glomeruli. Proportionately, about 10 cc out of 2000 cc of water, ten to fifteen grams of 1100 gm. of chlorides, fifteen to twenty-five grams of 48 gm. of urea, and none of 270 gm. of glucose reach the renal pelvis. The test of renal function, which is the simplest, is the estimation of the specific gravity of the last twelve hours' urine excretion during a 24-hour period of taking only solid foods. Under this condition a specific gravity lower than 1.026 indicates renal damage. The average normal range is 1.028 to 1.034. Glomerular filtration rate is estimated by using substances which are filtered in the glomerulus and not secreted nor re-absorbed. Mannitol and inulin are two such substances. By this type of test it has been determined that glomerular filtration remains very constant at a rate of one hundred and thirty cc per minute. Tubular function is most complex. In the proximal tubules glucose

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and electrolytes are rapidly re-absorbed, whereas substances such as the antibiotics and chemotherapeutic agents are excreted. If the tubular cells are overloaded with a substance which they are absorbing, antibiotics are blocked and remain in the blood longer. To estimate tubular function, any substance which is excreted in the urine may be utilized either in the form of so-called clearance tests or cellular function tests. By using such substances as urea, para-aminohippurate, potassium and so forth in normal concentration, the amount of these substances excreted in one minute indicates the tubular blood flow. When these substances are given in amounts which are over the average and overload the tubular cells, the amount excreted *indicates the tubular cell function capacity rather than* the tubular blood flow tests. Dyes such as phenolsulfonphthalein and indigo carmine are excreted by the tubules, but do not serve to indicate any change in renal function unless there has been severe renal damage. Cystoscopically these substances serve to demonstrate obstruction in the upper tract or variations in the degree to which the vascular bed is dilated, constricted or sclerotic. If the proximal tubule was the end of renal cell tubule function, the amount of urine per day would be about thirty-five liters. The proximal and thin segments re-absorb so much water that an estimated one hundred and six cc of 130 cc glomerular filtrate reach the distal tubules. If, during its course through the thin segment, the filtrate is rich in solutes such as sodium, potassium, ammonium salts or glucose, less water can be absorbed, so we see diuresis. When the tubular fluid traverses the distal tubules, water and salt are re-absorbed. The re-absorption of salt is influenced by the posterior pituitary and hypothalamus. The adrenal steroids modify this salt re-absorption also. The sodium blood level also influences absorption. The lower the blood level, the more absorption. If the blood level is high we see excretion. The glomerular filtrate starts as an alkaline solution. When it traverses the distal tubule the basic ions are absorbed and ammonium, the end product of the action of carbonic anhydrase on glutamine in the tubular cells, is secreted. Damage to this mechanism results in renal acidosis due to the reduced re-absorption of the basic ions.

Lederle has produced a carbonic anhydrase inhibitor which acts as a diuretic and among other things as an alkalinizer. The chemical is two acetylamino one, three, four; thiadiazole five, sulfonamide 6063. Carbonic anhydrase alkalinizes the urine by converting carbon dioxide and water into carbonic acid in the tubular cells. The ionization of carbonic acid to form hydrogen ion and bicarbonate ion is indirectly dependent upon carbonic anhydrase activity. The hydrogen ions so formed take the place of the sodium ions of the buffers of the glomerular filtrate, chiefly disodium phosphate and sodium bicarbonate. The excretion of sodium acid phosphate in the urine conserves sodium which returns to the blood. The carbonic acid diffuses back into the blood. The formation of ammonium ion, which also conserves base by buffering nonvolatile strong acids, is also dependent on the supply of hydrogen ions. When carbonic anhydrase activity is inhibited by diamox, less hydrogen ion is available for the acidification process. The sodium ion of the buffers no longer replaced by hydrogen ion is excreted. Filtered bicarbonate ion, no longer forming carbonic acid in the lumen, is also excreted. Thus the urine contains sodium bicarbonate after diamox. This action provides possible chemical application in uric acid excretion control. At the same time, the lack of hydrogen ion decreases the formation and excretion of ammonium. This takes fluid and sodium of the tissues, producing diuresis.

One internal secretion function of the tubular cells involves the elaboration of renin, a proteolytic enzyme, when anoxia occurs. Renin acts on the liver produced renin substrate known as hypertensinogen to form a pressor substance, angiotonin or hypertensin. The internal secretion function, as compared to excretory function, is controlled by the blood chemical pattern. Selye has produced changes in the kidneys of cats and dogs which decrease glomeruli and tubular lumens to such an extent that the kidney approaches the status of a solid glandular organ. A decrease in phosphatase content of renal cells has recently been shown to indicate early renal damage. Greenstein is engaged in studying the amino acid composition of renal cells by varying centrifugation speeds. He feels that the amino acid metabolism of renal cells is more complex and elastic than that of hepatic cells. Study of ground substance is also occupying considerable attention. Metabolism of this tissue is also related to renal function.

In conclusion, metabolic aspects of renal physiology are being demonstrated to be infinitely more complex than heretofore realized.

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COAGULUM PYELOLITHOTOMY

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Between 1943 and 1946, I made several publications[1–5] describing the use of a fibrinogen coagulum in removing renal stones at open operation. No recent publications have been made, not because of ineffectiveness of the procedure, but because of the fact that one of the materials essential for its performance has not been procurable.

Briefly the technique consists of the simultaneous injection of fluid thrombin and fibrinogen through a catheter into the renal pelvis at open operation. Five minutes after injection a firm, tenacious coagulum forms which incorporates within itself all free calculi present within the pelvis. Withdrawal of the coagulum through a pyelotomy incision should theoretically remove all free stones from the kidney. It could not be expected to remove a stone trapped in a calyx whose infundibulum was of lesser caliber than the diameter of the stone, nor could it be expected to enmesh stones imbedded in or adherent to the wall of the pelvis. A narrow intrarenal pelvis likewise forms a contra-indication for pyelolithotomy of any type

Advantages inherent in this type of surgical removal of renal calculi are several Only minimal exposure and liberation of the kidney are carried out as access to the renal pelvis and upper ureter is all that is necessary for the procedure All free stones, regardless of size, number, or location should be removed enmeshed within the clot. Fragmentation of calculi during removal is avoided; trauma to the kidney is reduced to a minimum; and radiolucent as well as unsuspected stones that did not show on x-ray should be removed. Most of the early work on this subject was carried out with fibrinogen obtained from human blood Generous supplies were made available through the Blood Fractionation Program at Harvard, from blood collected by the American Red Cross At the end of World War II, however, this source became no longer available, and one of the commercial companies attempted to process human fibrinogen for use in this operative procedure. Many of their preparations were excellent, but others were technically unsatisfactory, and they abandoned attempts to produce this material.

Read at annual meeting, American Association of Genito-Urinary Surgeons, Shawnee-on Delaware, Pa May 26–28 1954

[1] Neurath, H , Dees, J E and Fox, H The preparation and properties of human fibrinogen solutions J Urol , 49: 497, 1943

[2] Dees, J E and Fox, H The properties of human fibrinogen coagulum Preliminary report J Urol , 49: 503, 1943

[3] Dees, J E The use of an intrapelvic coagulum in pyelolithotomy Preliminary report South Med J , 49: 503, 1943

[4] Dees, J E Fibrinogen coagulum as an aid in the operative removal of renal calculi J. Clin Invest , 23: 576, 1944

[5] Dees, J E The use of a fibrinogen coagulum in pyelolithotomy J Urol , 56: 271, 1946

In 1951, Moore and Sweetser[6] reported 7 cases in which they had carried out coagulum pyelolithotomy successfully, using bovine fibrinogen. This material was supplied to them by another drug company, but when contacted, this company was unwilling to attempt to produce bovine fibrinogen on a commercial basis or to supply additional amounts for experimental purposes. During the past year and a half, I have been working with another laboratory* which has produced uniformly satisfactory preparations of bovine fibrinogen. Even they, however, are hesitant about attempting to market the product as they find it impossible to estimate the demand that there may be for it. They have, however, promised to make available to as many members of this group as possible a limited supply of fibrinogen for clinical trial.

Although the materials are used topically rather than parenterally, the possibility of allergic reaction to minute quantities of bovine fibrinogen which might be absorbed must be considered. With this in mind, slightly over 100 allergic and nonallergic patients were skin-tested to bovine fibrinogen, and in this group only two individuals showed a slight delayed positive reaction. In one patient, coagulum pyelolithotomy was carried out on the right kidney, and 5 weeks later, the same procedure was performed on the left kidney without evidence of any sensitizing reaction having occurred. In none of the clinical cases has there been any evidence of allergic or other type of reaction to the bovine material.

One factor that hampered the marketing of human fibrinogen was the difficulty in sterilizing it of hepatitis virus. This disease is not known to exist in cattle, and should present no problem with the bovine product. If and when placed upon the market, the bovine material should be less expensive than the human, if blood had to be purchased by the manufacturer.

In vitro studies on bovine fibrinogen show it to be practically identical with human fibrinogen so far as its biological and physical properties are concerned. Strong, tenacious coagula are produced within five minutes after mixture with appropriate concentrations of bovine thrombin. The resulting coagula spontaneously disintegrate in human urine within twelve to eighteen hours due to the action of urinary proteolytic enzymes. Coagula made from one batch of fibrinogen before and after being kept at ice box temperature for approximately one year showed no appreciable change in physical characteristics. Once the dried material is dissolved, however, denaturation commences within three or four hours, and within 24 to 48 hours, properties of coagulation are very adversely affected.

One interesting observation has been made on the use of Ringer's solution as a solvent for the dried fibrinogen. Normal saline was used as the solvent for human fibrinogen but the initial coagula made from bovine fibrinogen dissolved in normal saline solution were of poor tensile strength (table 1). It was noted that cylindrical coagula 8 mm. in diameter made from 8 per cent fibrinogen dissolved in saline and coagulated with 25 to 50 units of thrombin per cc produced coagula with tensile strengths at the end of five minutes ranging from 30

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[6] Moore, T. D. and Sweetser, T. H.: Coagulum pelviolithotomy: An improved technique. J. Urol., 67: 579, 1952.

* Bovine fibrinogen has been supplied through the courtesy of Dr. M. C. Wynes, Armour Laboratories, Chicago, Ill.

TABLE 1. *Effect of various diluents on tensile strength of fibrinogen coagula*

	8% Fibrinogen in					
	H_2O		Saline		Ringers	
Thrombin, u/cc	25	50	25	50	25	50
Tensile strength, grams	29	45	31	35	125	145
Control, grams	23	41	21	27	127	162

TABLE 2. *Effect of various diluents on coagulum properties*
8% fibrinogen and 25 u. thrombin/cc

	Diluent							
	0.03% KCl	0.033% $CaCl_2$	0.03% KCl 0.86% NaCl	0.03% KCl; 0.033% $CaCl_2$	0.86% NaCl, 0.033% $CaCl_2$	0.86% NaCl	Ringers	H_2O
Tensile strength, grams	27	40	25.5	49.5	99	26	126	26
Stretch, inches	6.5	2.0	6.75	2.5	1.5	7.0	1.0	6.5

to 35 gm. When Ringer's solution was substituted as a solvent, and the other conditions were unchanged, coagula with tensile strengths ranging from 125 to 160 gm. were obtained.

When coagula were made with the individual components of Ringer's solution as solvents, as well as from various combinations of these components, it appeared that the calcium ion was of more importance than either the sodium or potassium ions in this respect (table 2). From these, as well as additional *in vitro* experiments, it was determined that 4 per cent fibrinogen by weight dissolved in Ringer's solution, coagulated by thrombin, 30 units per cc dissolved in normal saline solution, gave optimum coagula at the end of 5 minutes, with tensile strengths ranging from 40 to 65 gm. with a stretch of the coagulum of 25 to 30 per cent before breaking.

Only slight modifications in the operative technique as initially published have been made. The renal pelvis and upper ureter are exposed through an appropriate flank incision. The ureter is temporarily occluded at the ureteropelvic junction by means of a small bulldog arterial clamp. Through a small incision in the pelvis, a round headed mushroom catheter, 14 or 16F in size, is introduced, and the pyelotomy closed snugly around its shaft with continuous fine chromic catgut. The catheter is then withdrawn so that its head impinges snugly against the wall of the pelvis. This modification is important, as it insures the most perfect irrigation and aspiration of the contents of the pelvis. Following aspiration of all urine, the capacity of the renal pelvis is determined by injecting saline or Ringer's solution through the catheter by means of a graduated glass syringe and noting by palpation and inspection the tension of the distended pelvis. After complete aspiration of the pelvis, it is irrigated with fibrinogen solution and aspirated. Then fibrinogen in an amount equal to 90 per cent of the predetermined capacity of the renal pelvis is injected through the mushroom catheter. Simultaneously, by means of a small graduated syringe and needle, an assistant injects thrombin,

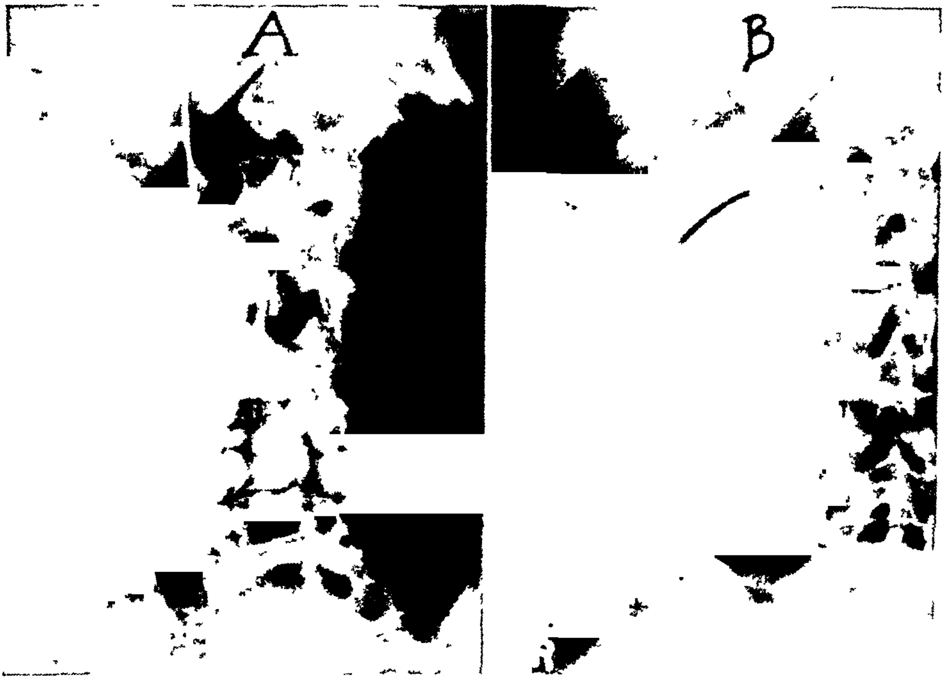

FIG. 1. *A*, preoperative films showing multiple stones in right kidney. *B*, postoperative film showing removal of all stones.

30 units per cubic centimeter, in an amount equal to 10 per cent of the pelvic capacity through the wall of the mushroom catheter into its lumen, so that the two solutions are intimately mixed as they enter the renal pelvis. After a lapse of 5 minutes, the pyelotomy incision is again opened and extended to a size adequate for removal of the resultant clot. The coagulum is then gently but firmly removed with ring forceps.

I would like briefly to show 2 cases illustrating the value of the procedure:

E. M. S. (Duke Hospital No. B 84744) had been hospitalized for 9 months because of severe encephalomyelitis which had produced almost complete muscular paralysis as well as a neurological bladder. Seven weeks previously, right flank pain, chills and fever had been relieved by means of an indwelling ureteral catheter which had been left in place since that time. X-rays (fig. 1) showed a calculus 5 by 10 mm. in diameter at the ureteropelvic junction and many small calculi scattered throughout the pelvis of the right kidney. Coagulum pyelolithotomy was carried out, with removal of the obstructing calculus and also 25 small calculi, varying from 1 to 5 mm. in diameter. Postoperative plain x-ray as well as x-rays made 1 year later showed no remaining or recurrent calculus (fig. 2).

V. M. (Duke Hospital No. B 17676) had passed several calculi from the right kidney during the preceding 6 years. For 7 months he had had recurrent attacks of kidney colic on the right without passage of a calculus. X-rays (fig. 3) showed a calculus measuring 1½ cm. in diameter in the midportion of the right ureter. Two faint small opacities were seen in the region of the right kidney pelvis. At operation, the ureteral calculus was removed through a ureterotomy incision directly over the stone and coagulum pyelolithotomy successfully removed the

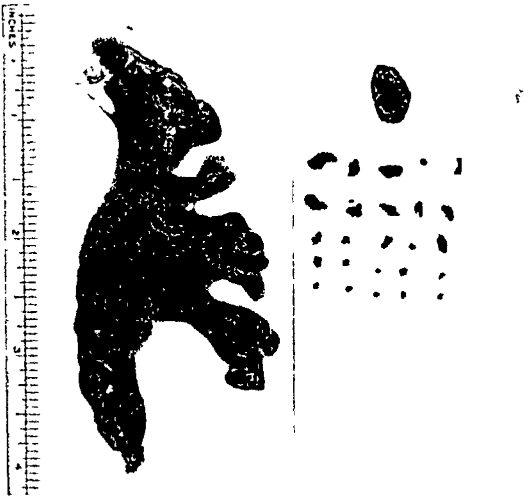

FIG. 2 Coagulum which removed all 26 calculi present

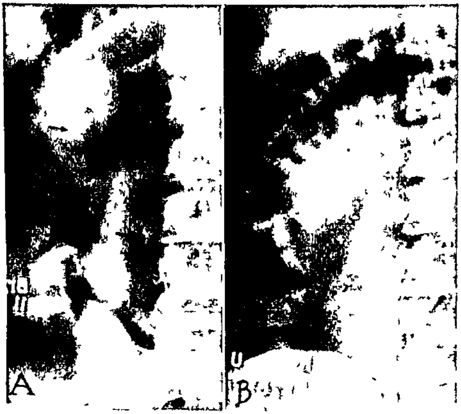

FIG. 3. *A*, showing one large ureteral and two small renal calculi *B*, postoperative film showing removal of all stones.

two tiny stones from the renal pelvis, one being about 6 mm. and the other 2 mm. in diameter (fig. 4).

The results obtained in 73 coagulum pyelolithotomies are shown in table 3. The 11 cases in group 4 of this table were instances where a single large stone was removed with forceps, and the coagulum technique then used in an attempt to remove undemonstrable additional stones. No such stones were removed, nor

FIG. 4. X-ray and photograph of coagulum which removed two small renal calculi. Ureteral stone removed separately.

TABLE 3. *Results in 73 coagulum pyelolithotomies*

	Fibrinogen	
	Human	Bovine
1. All demonstrable stones removed	22	8
2. All demonstrable, as well as previously undemonstrable stones removed	5	
3. All stones not trapped in calyx or adherent to mucosa removed	6	1
4. No free stone present; none removed	7	4
5 Some, but not all, free stones removed	8	3
6 Free stones present; none removed	2	
7. Technical failure	7	

were any detected in this group on subsequent x-ray. The technique was only partially successful in the 11 cases in group 5, but here, as well as in the other instances where the coagulum failed to remove all stones, practically all of the remaining stones were subsequently removed either by forceps through the pyelotomy, or through a nephrotomy incision. It is felt that in employing this technique the operator has nothing to lose except ten or twelve minutes of operating time. If the procedure is unsuccessful, one can then proceed to search for the stone in the usual manner. If the procedure is successful, the operating time is often considerably reduced; and certainly there have been many stones removed by the coagulum in this series of cases that, in my opinion, would have been impossible to remove by the usual methods of pyelolithotomy.

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DIAGNOSIS AND TREATMENT OF HYDRONEPHROSIS

VINCENT J. O'CONOR

It would seem that so much has been written and said in recent years about the diagnosis and treatment of hydronephrosis that any additional remarks at this time would seem redundant and unimportant.

Four years ago I reported upon the results obtained in the conservative treatment of hydronephrosis due to unilateral or bilateral obstruction at the ureteropelvic junction.

Dilatation of the upper urinary tract or "urinary trees" has been termed "hydronephrosis" and "hydro-ureter" even though these are loose and rather inaccurate terms. As Braasch has so consistently emphasized, it might have been better if dilatation of the pelvis and calyces had been designated as "pyelectasis" and dilatation of the ureter as "ureterectasis". However, it seems useless to even consider changing terms at this late date.

In America we believe that most instances of dilatation in the urinary tract are the result of obstruction. We all recognize many instances of ureteral and renal pelvic dilatation that exist in the absence of evident obstruction, but the causal factor involved in these cases is often obscure and incomplete. The European pathologists of a generation past summarily dismissed this discussion by explaining these dilatations as being the result of either "faulty innervation" or "congenital overgrowth of tissue." In fact, both Stoerk and his successor, Bauer of Vienna, called our descriptions of obstructive lesions of the ureter and renal pelvis "the American disease." This meant, of course, that they did not believe in what we term "mechanical" causes of obstructive uropathy. Actual proof of their own theories was never evident.

Our discussion today supposedly eliminates consideration of the group of patients in whom the hydronephrosis has been referred to as "inflammatory", "neurogenic", "atonic" or "functional." Yet, in reviewing the diagnostic possibilities which might precede the indications for surgical correction, one must constantly keep all of these types in mind.

The best and oldest method of demonstrating the presence of retained urine within the renal pelvis is by the passage of a ureteral catheter. If the rapid and excessive flow of urine occurs only after the catheter has been passed 25 to 28 cm. beyond the ureteral orifice (in the adult), one presupposes an obstructive lesion at the ureteropelvic junction. If a rapid flow of urine takes place when a shorter amount of catheter has been introduced, it is understood that either both ureter and pelvis are dilated, or the dilated pelvis is that of an ectopic kidney.

With the widespread use of excretion urographic studies, many unsuspected instances of varying degrees of hydronephrosis are being discovered It is often

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Read at annual meeting, American Association of Genito-Urinary Surgeons, Shawnee-on-Delaware, Pa. May 26–28, 1954.

difficult to distinguish between the large normal pelvis and an early hydronephrosis. In the former, the minor calyces are not flattened, clubbed or dilated, whereas the early hydronephrotic calyces always show distortion from the usual umbilicated outline. A film made with the patient in the upright position will frequently show a "flattening" of the renal pelvis outline representing a "fluid level" in the hydronephrotic kidney. This does not occur in the large normal pelvis. The "delayed" picture, both after excretion and retrograde pyelography, is the most diagnostic roentgenological evidence of urine retention. Excretion urograms are often misleading. A single set of films should never be accepted as demonstrating the exact, all time physiologic or anatomic condition of an apparently obstructed upper urinary tract. This is especially true if a picture seems to indicate an obstruction at the ureteropelvic junction when the ureter, itself, appears to be dilated. I have twice had the unhappy experience of cutting down on a kidney when I had been misled by a single set of urograms to believe that we were dealing with an obstruction at the outlet of the renal pelvis. In both cases, the point of narrowing was in the lower ureter. The reports of Charles M. Stewart[1] and R. G. Bunge[2] on "Delayed Cystograms" furnish additional reason for careful and repeated observations in the study of hydronephrosis. These authors describe an amazing dilatation of the outline of ureter and renal pelvis in certain patients in whom previous excretion urograms had appeared normal. Their only explanation of this is an unusual ureteral reflux or regurgitation occurring when the bladder is filled with urine.

Once it has been definitely established that there is a noticeable dilatation of the renal pelvis due to obstruction at the outlet, it is important to decide whether this condition should be kept under repeated observation for some time or whether corrective surgery should be advised. Important factors in this decision will depend upon the presence or absence of pain; of urinary infection or "secondary" calculi; presence or absence of reflex symptoms such as anorexia, nausea or gastro-intestinal irritability. The majority of these patients do not present a problem of emergency and surgery should only be advised when the situation is crystal-clear as to the diagnosis.

The conservative treatment of hydronephrosis due to obstruction at the ureteropelvic junction may be one of watchful waiting or one of elective surgical correction. The patient may be carefully watched for a period of months, or even years if no untoward symptoms develop and the excretion urographic outlines remain unchanged. The urine should be examined frequently and blood chemistry studies done periodically.

If pain, infection of the urine, or reflex abdominal symptoms develop, surgery should be advised.

In 1950,[3] I reported the results of 98 plastic procedures on 88 patients. Since then, we have performed 37 additional operations on 32 patients. I have not conducted an additional critical review of this material for this paper. There were no deaths in the added series and nine of the patients had bilateral disease.

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[1] Stewart, C. M.: Delayed cystograms. J. Urol., **70**: 588–593, 1953.

[2] Bunge, R. G.: Delayed cystograms. J. Urol., **71**: 427–434, 1954.

[3] O'Conor, V. J.: Conservative surgery of hydronephrosis. N. Y. State J. Med., **51**: 503–505, 1951.

In four of these, the opposite kidney, which was relatively functionless, was removed after a successful pyeloplasty on the opposite kidney.

Technical improvements in some patients resulted from newer procedures.

One of these was the utilization on two occasions of the "pelvic flap" operation suggested by Ormond Culp[4] in 1951. An almost identical procedure was advised by P. L. Scardino and C. L. Prince[5] in 1953.

The Deming[6] procedure, with the use of the ureteral T tube for a drain, and splint was applied successfully to two patients. This is a valuable technique in an occasional patient, but it, like the Davis intubated ureterotomy, should be reserved for patients who cannot better be relieved by some type of flap or Y plasty procedure.

The Davis procedure proved to be the only procedure that could be applied in one patient with an elongated narrowing of the upper ureter. The result was most satisfactory in this patient. Unfortunately, this procedure is being widely employed by a number of inexperienced operators and we have had the experience in the past 5 years of being obliged to remove 4 kidneys subjected to this procedure elsewhere from 6 months to 2 years before we were consulted. A study of the original preoperative pyelograms suggested that a posterior Y plasty or flap procedure might have been better suited to solve the problem in these patients. We are greatly indebted to D. M. Davis for originating and popularizing intubated ureterotomy, but we feel that the operation should be reserved for the type of obstruction for which he originally recommended it. Mathé,[7] in 1953 described a technique similar to that of Davis and reported good results in 26 patients.

I still wish to advise caution in the ligation of arteries associated with hydronephrosis. It is true that the majority of these are aberrant and anomalous and supply a small or insignificant amount of renal tissue. However, a sufficiently large number are in kidneys which have a bipolar blood supply with no central or hilar vessels present. Approximately half of the renal substance is supplied by this divided arterial and venous system. In the past 2 years, I have been called in consultation twice where a kidney had to be removed after ligation of the lower vessels had been performed for relief of pelvic pressure. Examination of both of these kidneys showed a massive lower polar thrombosis and a congenital bipolar arterial supply. Engel[8] in 1951 reported no ill effects after ligation of an obstructing aberrant artery to the lower pole of the kidney in 21 patients. This procedure is safe only in a kidney which enjoys a central blood supply.

The use of polyethylene tubing may decrease the chance of encrustations forming during the 14 to 21 days of renal drainage. We have found that daily subcutaneous injections of 300 units of hyaluronidase keeps the urine clear and prevents lime salt deposits in most patients. Since the presence of the nephrostomy or pyelostomy tube is invariably accompanied by infection with Pseudomonas aeruginosa (B. pyocyaneus), we routinely use frequent catheter instillations of 15 to 30 cc of 0.1 per cent aerosporin solution. This has appeared to be a valuable addition to postoperative care.

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[4] Culp, O. S. and DeWeerd, J. H. Pelvic flap operation for certain types of ureteropelvic obstruction. Preliminary report. Proc. Staff Meet., Mayo Clin., **26:** 483–488, 1951.

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SUMMARY

The surgical relief of hydronephrosis due to obstruction at the ureteropelvic junction is rarely a problem of emergency except when stone or acute infection complicates the condition.

A careful diagnostic study of both kidneys is always indicated and repeated examinations are often advisable and necessary to obtain accurate diagnostic information.

Many patients with varying degrees of hydronephrosis can be safely kept under observation for prolonged periods of time if the condition is not progressive and pain, infection or reflex symptoms do not occur. Intelligent co-operation between patient and surgeon is presupposed in this regard.

When surgery is indicated, the operator should be prepared to correct the anatomical defect by the technique best suited to the problem at hand. The type of operation should be suited to the individual patient.

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PARTIAL RESECTION OF KIDNEY FOR TUBERCULOSIS

JOHN K LATTIMER

Partial resection of the diseased kidney was first done deliberately in 1887 Early operators attempted to apply this operation to carcinomas of the kidney, tuberculosis of the kidney, polycystic disease and many other then unsuitable conditions, with most unhappy results Following the operation there were many complications, such as urinary fistulas, hemorrhage and infection In more recent years, following the researches of Herbst and several other members of this organization, who devised safer methods for suturing the kidney substance, more effective control of urinary infections and more precise operating techniques, the procedure has become much more safe Partial nephrectomy has an excellent record in the literature It has found its widest use in the removal of calyces which contain stones, where the neck is strictured or the walls of the calyx diseased In a review of partial nephrectomies reported in 1950, Abeshouse presented figures which indicated that partial nephrectomy was a safer and less complicated operation than other operations for calculi such as nephrectomy, pyelolithotomy or nephrolithotomy His mortality and morbidity statistics are shown in table 1 This sanguine view of the operation may be due to the fact that the patients were a highly selected and favorable group of "good risks "

The technique of the operation has several possible variations A flap of kidney substance can be left along the lateral border of the kidney and subsequently folded over to cover the stump of the calyx, which was cut off and carefully sutured with atraumatic chromic catgut Another technique takes a wedge out of the diseased pole of the kidney, so that the sides of the wedge can be approximated over a pad of muscle or fat, for hemostasis The wedge can be run transversely or from front to back Any mattress sutures which approximate the kidney substance should include capsule and be "bolstered" with fat pads so they will not cut through

PARTIAL NEPHRECTOMY FOR TUBERCULOSIS

In the years before streptomycin (1946) a calcified tuberculous lesion was occasionally excised inadvertently in the belief that it was a stone in a calyx This mishap was all too often followed by a urinary fistula or a tuberculous wound infection, and occasionally it resulted in a miliary spread of the disease with death of the patient As recently as 1950, tuberculosis was listed as a contra indication for partial nephrectomy

With the advent of effective antituberculosis chemotherapy, however, Semb in Norway, Rinker in the United States and others in Europe again undertook the operation, under the protection of the antituberculosis drugs We began doing this operation for tuberculosis in 1951 on patients whose disease was refractory to streptomycin

Our own technique for resecting tuberculous portions of the kidney differs

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TABLE 1. *Complications after operations for stone*
(Abeshouse, 1950)

	Operative Deaths	2° Hemorrhage	Urinary Fistula	Recurrent Stones
	%	%	%	%
Partial nephrectomy	2.6	3.1	1.5	2.0
Pyelolithotomy	2.4	4.0	4.1	11.0
Nephrolithotomy	9.8	10.5	12.5	15.0
Nephrectomy	6.3			

from the "wedge" type of resection in that we cut the kidney off squarely, well below the infected area, leaving no flaps of tissue which might become necrotic and thus act as culture media for any residual M. tuberculosis. It is our practice to first slit the capsule over the involved pole of the kidney and strip it well back. In this way the indentations, scars or caseous areas which mark the tuberculous lesions can be seen, and the line of excision placed well proximal to them.

It has been our experience that exact localization of the tuberculous kidney lesion has been determined fairly accurately beforehand from multiple retrograde and intravenous pyelograms. Their location can be verified after the kidney capsule is stripped back, exposing the surface of the kidney. There is most commonly an indentation where the pyelogram showed an involved calyx.

A cobbler's stitch is placed across the kidney at the anticipated line of excision, in order to reduce the chance of squeezing tubercle bacilli into the blood stream during the handling of the kidney at operation. A soft, rubber-shod intestinal clamp is applied to the renal pedicle for periods not exceeding ten minutes. It is released for one minute every ten minutes and the bleeding sponged until the clamp is re-applied. With the handle of a blunt knife the kidney parenchyma can quickly be broken through along the line of the cobbler's stitch until the firm blood vessels are reached. These can be individually clamped and ligated to a certain extent. When the neck of the calyx is exposed, this can be wiped clean by blunt dissection and cut across. The stump is then carefully sutured with a running suture of atraumatic, 5-0 chromic catgut. A pad of fat or muscle is sutured over the stump to prevent leakage. The kidney pedicle clamp, which has been applied intermittently up to this point, is then removed so as to not embarrass the kidney blood flow further. The assistant's thumb and forefinger can compress the kidney just below the suture line to control residual bleeding. Additional bleeding points can then be secured with small suture ligatures, which are used to pull pads of fat down over the ends of the small bleeding vessels.

Chemotherapy for tuberculosis is started 4 months before partial nephrectomy, is intensified on the day of operation and is continued for an additional 8 months after the operation, in order to complete at least one year of combined chemotherapy. The chemotherapeutic program which is employed, as of 1954, consists of streptomycin 1.0 gm. twice weekly, isioniazid 100 mg. 3 times a day and sodium PAS 5 gm. 3 times a day. These drugs are given together for a period of one continuous year.

Aortography and angiography are of limited practical value in determining the extent of the kidney lesions. They do help occasionally in determining whether or not the main arteries of the kidney are distributed in such a manner as to permit resection of the infected area. If the main artery enters the infected portion first and then goes to the good portion, it may be impossible to resect the diseased portion without jeopardizing the circulation to the remainder of the kidney.

Follow-up results in converting the urine from positive to negative after partial resection of the kidney for tuberculosis have been promising, at least at the 2-year point. Dr. Carl Semb of Oslo, Norway has done 87 cases and reports a 90 per cent conversion rate at the end of 2 years. Many of his failures were due to tuberculosis of the prostate and were not the result of failure of the operation on the kidney. Dr. Semb has had no deaths among his cases but he has had severe reactions resulting from clamping the renal pedicle for too long a period. Others have reported deaths. He now hopes to use his assistant's thumb and forefinger to compress the circulation during the entire operation, in order to prevent hemorrhage and at the same time permit the circulation of the remainder of the kidney to remain relatively normal throughout the procedure. Some of Dr. Semb's patients had extensive lesions, and the chemotherapy which they received was not as intensive as our cases now receive.

Our own bacteriological follow-up shows the results in 5 patients (table 2) all of whom were operated upon at least two years ago and all of whom have negative urines. All of these men have received antituberculosis chemotherapy after operation. One man had a brief episode of hematuria one year after the operation and was given additional chemotherapy, even though his urine culture did not become positive. We have had no urinary fistulas, but it is our observation that some leakage of dye from the cut calyx can often be observed during the first 3 weeks after operation if retrograde pyelography is done. Examination of kidneys post mortem, which had been operated on some months earlier by the same technique but for calculous disease, revealed a normal appearing renal capsule from which the pathologist could not determine that any operation had ever been done on the kidney.

It is our belief that if the visible tuberculous lesions are resected, any residual lesions which are in the parenchyma, but not visible by urography, are usually small enough to be arrested by the year of chemotherapy which is given concurrently with the operation.

TABLE 2. *Partial nephrectomy for TB follow-up, 5 cases*

Name	Date Partial Nephrectomy	Chemo ℞ Coverage	Time Negative Since Operation
G. T.	May 51	16 mos	3 years
J. L	May 51	4 mos	3 years
C B.	November 51	4 mos	2½ years
S V	March 52	3 wks	2 years
A A	May 52	17 mos	2 years

Medical treatment of kidney tuberculosis, even of large cavitary lesions, has now become so effective that it has sharply curtailed our surgical program of partial nephrectomies, at least temporarily. We had assembled some thirty cases that were suitable candidates for partial nephrectomy in that the disease was limited to one segment of the kidney. We operated upon five of these cases in rapid succession and were prepared to go on to the others, when we discovered that all of the other twenty-five had been converted from positive urine cultures to negative, by one year of chemotherapy. We are now waiting to see if these patients relapse before we proceed with any further surgery. At the end of 2 years none of them have yet broken down, so that we are not extending our series of partial nephrectomies further at this time. As a technical maneuver, however, the operation of partial resection of the kidney for tuberculosis is entirely practical, should chemotherapy fail.

SUMMARY

Partial nephrectomy for tuberculosis should differ from partial nephrectomy for other causes in the following particulars:

The active tuberculosis must be confined to only one segment of the kidney. It must not have spread to adjacent areas of the renal pelvis or calyces.

The vascular supply of the kidney must be located in a position which will permit resection of the diseased area.

Any pulmonary, osseous, or lymphatic tuberculous foci elsewhere in the body should be quiescent before partial nephrectomy is attempted.

Prolonged and intensive preoperative and postoperative chemotherapy should be given to reduce the activity of the tuberculous lesions.

Manipulation of the tuberculous portions of the kidney should be strictly avoided while freeing the pedicle and excising the tuberculous areas.

The renal capsules should be peeled back liberally in order to reveal the true extent of the tuberculous areas.

The renal pedicle should be occluded intermittently by a soft, rubber-shod intestinal clamp, by the surgeon's fingers or by a tourniquet, during the actual manipulation of the kidney. This will help to prevent the dissemination of tubercle bacilli into the blood stream during the operative procedure.

The advent of streptomycin and PAS therapy for renal tuberculosis has reduced the incidence of fistula formation and of fatal miliary dissemination of the tuberculous disease to a point where partial nephrectomy for tuberculosis is now a practicable procedure. The operation is applicable, however, only to a few highly selected cases.

The success of this operation in the hands of Semb and others, verified by our own observations, leads us to believe that partial resection of the kidney, in conjunction with proper chemotherapy, does have a particular place in the treatment of certain cases of kidney tuberculosis.

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BILATERAL RENAL PAPILLOMAS: TRANSPELVIC ELECTRO-RESECTION WITH PRESERVATION OF KIDNEY. CONTRALATERAL NEPHRECTOMY; FOUR-YEAR SURVIVAL

J. A. CAMPBELL COLSTON AND JOHN A. ARCADI

From the James Buchanan Brady Urological Institute, the Johns Hopkins Hospital, Baltimore, Md.

Over 110 years ago Rayer described what apparently was the first case in which bilateral renal pelvic tumors were found. Since that time only five other proven cases of this condition have appeared in the world medical literature, two of which were reported in the American literature. (These are the cases of Sanford and of Gibson.) In two other cases the diagnosis is presumptive on clinical findings only. In those patients operated upon, the initial operation was invariably a nephrectomy. In all cases, except that described by Gibson, subsequent treatment was directed towards palliation only. No definitive surgical attack was made on the contralaterally involved kidney.

In 1930, H. L. Sanford presented a case of bilateral renal pelvic carcinoma. His patient was a 56-year old man who had had hematuria. Radiographic investigation revealed what apparently was a tumor in the right kidney and a suspicious area in the pyelogram of the left kidney. Profuse bleeding from the right kidney necessitated nephrectomy. A papillary transitional cell carcinoma was found. The patient did well immediately after operation and seemed to improve slightly. However, over the subsequent three weeks, uremia developed and death followed. The left kidney was obtained for examination and a transitional cell carcinoma was found which involved the renal parenchyma and pelvis.

The case described by Gibson was that of an 86-year old man who 14 years previously had had a nephrectomy for a papillary carcinoma of the renal pelvis. He was seen because of hematuria of 24-hours' duration. The blood was found to be coming from the remaining kidney. The kidney was explored and a grade 1 papillary carcinoma was found in the pelvis. This lesion was excised, and continuity restored by pyeloplasty. The patient's postoperative course was uneventful. Two years later he reported to Dr. Gibson that his health had been splendid. The patient has no symptoms, and his urine has remained clear.

Our own case bears some resemblance to Dr. Gibson's patient, but certain features of our patient's history and clinical course are so unique that they will be reported in detail.

The patient was a 57-year old housewife who was first admitted on August 21, 1950, because of intermittent, painless hematuria of 5 months' duration. In 1943 an abdominal hysterectomy was performed elsewhere for fibroids. Apparently the right ureter was injured and a ureterovaginal fistula drained for about four months, but no diagnostic procedures to determine the location of the injury were carried out and no operation was performed. After the vaginal drainage of urine ceased, excretory urograms revealed no function of the right kidney; the

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left kidney was considered normal. The patient had no flank pain except for one episode of "right pyelitis" shortly after the hysterectomy. Until March 1950, the patient was in good general health. At that time, she had an episode of painless hematuria lasting about 8 hours. A left retrograde pyelogram revealed a filling defect in the lower portion of the renal pelvis. Five subsequent episodes of hematuria followed the initial one. Retrograde studies were repeated, revealing an apparent increase in the size of the filling defect. The patient was then referred for evaluation and therapy.

Physical examination was essentially normal. The left kidney was palpable but not tender. The right kidney could not be felt. Excretory urograms showed a filling defect and distortion of the middle calyx of the left kidney which were interpreted as typical of a papillary pelvic tumor. The hemogram and blood chemistry studies were normal. An occasional white cell and one to two red cells were seen in the centrifuged urine specimen. A trace of albumin was also noted.

On August 23, 1950, through a left flank incision, a pelviotomy was performed and a raspberry-like, sessile tumor was found. Cephalad to this tumor, a smaller pedunculated tumor was noted. Both tumors were excised with the cutting current. The bases were then thoroughly destroyed with the coagulating current. A 25 per cent solution of podophyllin on cotton swabs was then applied to the tumor-bearing area in the hope of destroying any tumor cells which might have survived the electrocoagulation. The bleeding was well controlled and the pelvic incision was closed with a continuous suture of 4-0 chromic catgut. Two Penrose drains were placed at the pelviotomy site and closure was routine. The patient tolerated the procedure well. The postoperative course was uncomplicated except that the flank wound drained urine for 4 days. The patient then started voiding in good quantities. There were no significant changes in the blood chemistries. She was discharged on the twelfth postoperative day in excellent condition, the incision firmly healed.

Histological examination of the tissue removed revealed a papillary tumor (fig. 1, *A*) composed of rather uniform, large cells arranged in sheets with scant cytoplasm and vesicular nuclei. Some of the fragments contain a few strands of smooth muscle and connective tissue in which tumor cells are seen to grow (fig. 1, *B*). The final diagnosis was papillary carcinoma of the renal pelvis.

Her subsequent course was followed closely by retrograde pyelograms. The films revealed no evidence of tumor recurrence. Some narrowing of the infundibulum of the inferior major calyx was noted shortly after operation, but this has remained unchanged in subsequent films.

The patient returned on November 27, 1953, complaining of a mass in the right side of the abdomen which she had first noted 3 weeks previously. She was admitted to the hospital, at which time the physical examination was essentially normal. The left kidney was not palpable or tender. In the right upper quadrant and extending to just below the umbilicus on the right was a large, smooth, freely movable, nontender mass, about 12 cm. in length and 8 cm. wide.

Blood chemistry studies and hemogram were entirely normal. The urine con-

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right rectus incision. A brownish-blue, retroperitoneal cystic mass was immediately noted. Minimal dissection revealed that this was a hydronephrotic kidney with a greatly dilated tortuous ureter. The mass was aspirated and about 200 cc thick brownish fluid was removed. Nephrectomy and partial ureterectomy were carried out without incident. There was no evidence of intra- or retroperitoneal metastases. The left kidney felt normal. The patient tolerated the procedure well and had a benign postoperative course. She was discharged on the tenth postoperative day in excellent condition.

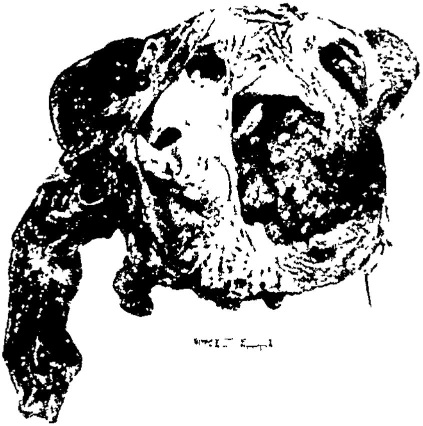

Fig. 2. Gross specimen of hydronephrotic right kidney showing tumor in upper portion of renal pelvis. No other tumors are seen in dilated pelvis or ureter.

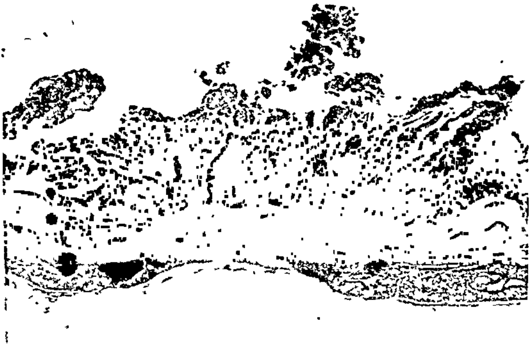

Fig. 3. Low power view of tumor of pelvis of right kidney. × 7½

Examination of the specimen revealed a large hydronephrotic sac containing chocolate brown fluid with virtually no remaining renal parenchyma. At the infundibulum of the superior calyx, there was a 2 by 2 cm. papillary tumor (fig. 2).

The histological section shows kidney pelvis in which there is chronic inflammation and thickening. Over a broad surface of the pelvis there is a papillary tumor, composed of fairly well differentiated cells piled up on slender connective tissue stalks (fig. 3). There is no direct invasion of the pelvis seen, although in a very superficial part of the mucosa directly beneath the tumor there are tumor cells within what appears to be a lymphatic (fig. 4). The capsule of the kidney appears normal, but the renal parenchyma is only one high power field in thickness. The final pathological diagnosis was hydronephrosis with papillary transitional cell carcinoma with no direct invasion seen.

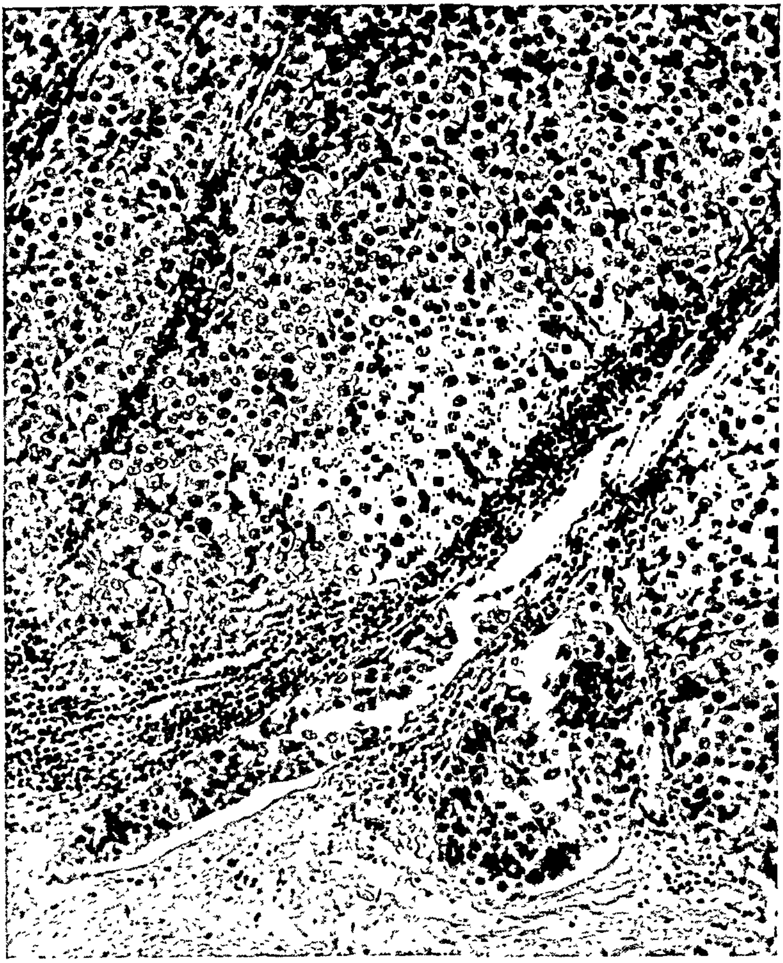

FIG. 4. High power view of tumor shown in figure 3. Tumor cells are seen within what appear to be lymphatics. × 150

DISCUSSION

The first tumor of the renal pelvis in this patient was manifested by total gross, painless hematuria. Routine urological diagnostic techniques were used to complete the diagnosis. Since the kidney involved in tumor was the only one functioning, electroresection was used to remove the tumor. The muscle invasion seen in this tumor indicates it was a papillary carcinoma rather than a "benign papilloma."

The nonfunctioning right kidney was asymptomatic and not palpable for many years. Its sudden increase in size was alarming, but in retrospect probably represented hemorrhage from the tumor. If the tumor had not produced bleeding, its discovery certainly would have been greatly delayed. Since no invasion of muscle was seen in this second tumor, the diagnosis of papillary carcinoma is equivocal. The finding of tumor cells in a lymphatic, however, strongly suggests that the tumor is a carcinoma.

The problem presented by this case and the result so far obtained emphasize the necessity of surgical exploration in all cases of solitary kidney in which a diagnosis of tumor is suspected. One of us (J. A. C. C.) has previously operated upon a case of tumor in a solitary kidney.

A 43-year old man entered the Johns Hopkins Hospital on August 26, 1947 because of several attacks of hematuria, one of which resulted in acute urinary retention from clots. As a result of urological studies carried out in his home town he was told that he had either a soft stone or a tumor of the right kidney and that there was no function from his left kidney.

On physical examination the patient was obviously anemic with pallor of his lips and mucous membranes. The right kidney was easily palpable, definitely enlarged, but nontender. The left kidney could not be felt. The examination revealed no other abnormalities.

Laboratory studies: Hemoglobin 8.8 gm. (60 per cent), white blood cells 6650, nonprotein nitrogen 48 mg. per cent, phenolsulfonphthalein excretion first ½ hour, trace; second ½ hour, trace; third ½ hour, 15 per cent; fourth ½ hour, 10 per cent; total 2 hours output 25 per cent.

An excretory urogram showed a moderate degree of hydronephrosis on the right side and no excretion from the left kidney. Retrograde studies revealed that phenolsulfonphthalein (phthalein) appeared from the right kidney in 8 minutes, with an excretion of 8 per cent in 30 minutes. No excretion of urine occurred from the left kidney in 30 minutes. The right pyelogram showed a moderate dilatation with a large, irregular filling defect in the lower infundibulum and calyx extending into the pelvis and middle calyx.

A diagnosis of papillary carcinoma of the pelvis of the right kidney was made. It was decided, however, to explore the left lumbar region to determine accurately the status of the left kidney.

After transfusions of whole blood to combat the anemia, the left lumbar region was explored on September 3, 1947. The ureter was normal in appearance, but ended blindly in a small mass of fibrous tissue in the kidney fossa opposite the third lumbar vertebra. Sections of this tissue showed microscopically a few ill-defined tubules but no glomeruli or identifiable kidney tissue could be seen.

The postoperative course was uneventful except that the nonprotein nitrogen rose to 92 mg. per cent.

On September 10, 1947 the right kidney was exposed through a lumbar incision. The surface was smooth and no nodules were present. A dilated pelvis was exposed, opened, and some yellowish necrotic tissue evacuated. A mass about the size of a golf ball was then felt apparently arising in the upper calyx. This tumor was removed as completely as possible by forceps and suction, and the pelvis then washed out with ether and alcohol in the hope of destroying any tumor tissue which had not been removed. A mushroom catheter was placed in the pyelotomy incision and the wound closed.

No postoperative complications developed and the patient's general condition steadily improved, the nonprotein nitrogen falling to 27 mg. per cent. The pyelostomy tube was removed on the twentieth postoperative day and there was no subsequent leakage of urine through the incision. The patient was discharged on the twenty-second postoperative day. Microscopic study of tissue removed showed clear cell adenocarcinoma (hypernephroma).

The patient continued to improve for 2 months, but then an abscess formed in the incision. The evacuation of the abscess was followed by drainage of urine which persisted until death from cachexia occurred 5 months after the operation.

Ferris and Daut in 1948 reported the case of a 61-year old man on whom a clinical diagnosis of papillary tumor of the pelvis of the right kidney associated with absence of the left kidney was made. At operation, "A papillary epithelioma could be seen arising from the posterosuperior aspect of the renal pelvis and extending 1 cm. into the upper infundibulum. The greater portion of the tumor was excised along with a small segment of the site of origin. The pathologist reported this tumor to be a papillary squamous cell epithelioma, grade 2 (Broders' method) with no obvious infiltration of the renal pelvis." The remaining portion of the tumor was thoroughly destroyed by electrocoagulation.

There were no postoperative complications, but the concentration of urea on discharge was 64 mg. per 100 cc blood. The patient remained well "until June 1953, at which time hematuria and hydronephrosis developed" and he died 7 years after operation.

Vermooten in 1950 reported the case of a 52-year old woman on whom a diagnosis of tumor of the left kidney was made. At operation a tumor 10 by 7 cm. was found occupying the midportion of the kidney and apparently well encapsulated. The tumor was completely excised with 1 cm. border of normal tissue. Hemorrhage was controlled by a rubber shod clamp placed on the vascular pedicle. Study of the excised tumor showed that it had been completely removed with a 1 cm. margin of normal kidney tissue. A diagnosis of clear cell carcinoma was made from the sections prepared for microscopic study.

Fifteen months later the pyelogram was normal except for obliteration of the middle calyces and there was no clinical evidence of recurrence. The patient was symptomatically normal In October 1950 chest x-ray showed three metastatic nodules in the left lung These were excised with uneventful recovery Left retrograde pyelogram showed the kidney to be normal with normal function She died the following June with pulmonary metastases There was no local recurrence

SUMMARY AND CONCLUSION

A case is presented in which a papillary tumor was successfully excised from the pelvis of an only functioning kidney This procedure was performed over three and a half years ago and antedates the procedure reported by Gibson by at least two years The contralateral, nonfunctioning kidney was recently removed and a papillary tumor was found in its pelvis The importance of operative exploration of any solitary kidney in which a clinical diagnosis of tumor is suspected has been emphasized

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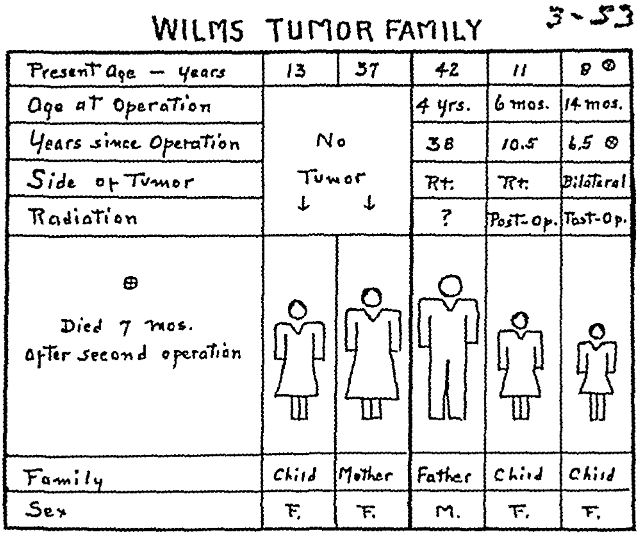
BILATERAL WILMS TUMOR IN A WILMS TUMOR FAMILY: CASE REPORT

W. L. FITZGERALD AND H. C. HARDIN, JR.

There is now a voluminous literature on embryonal or so-called Wilms tumors and a restatement of the commonly-described features of the disease would be superfluous here. Composite tumors and tumors described as sarcomas, occurring mainly in the infant and childhood age groups, are described in the literature previous to Wilms' publication in 1899.[1] This contribution however seemed to establish the concept that "the morphology of these tumors is so variable that no single description will apply."[2] The embryonal or mixed-cell type of tumor of the kidney is now known to occur in older children and is not infrequently reported in adults.[3-5] It is evident from a study of the literature that, the tissue pattern of these tumors being variable, likewise their degree of malignancy, proclivity for metastasis, sensitivity to x-ray and survival period of the victims also will be variable. Uncommon is the report of bilateral involvement and very *rarely* is there mention of a familial tendency in the occurence of Wilms tumors. Our case is reported because it was both bilateral and occurred in a Wilms tumor family (fig. 1).


WILMS TUMOR FAMILY 3-53

Present Age – years	13	37	42	11	8 ⊕
Age at Operation	No Tumor ↓ ↓		4 yrs.	6 mos.	14 mos.
Years since Operation			38	10.5	6.5 ⊕
Side of Tumor			Rt.	Rt.	Bilateral
Radiation			?	Post-Op.	Post-Op.
⊕ Died 7 mos. after second operation					
Family	Child	Mother	Father	Child	Child
Sex	F.	F.	M.	F.	F.

FIG. 1. Family chart

CASE REPORT

L. D., a white girl aged 14 months, was first seen April 14, 1947, being referred by a pediatrician. General abdominal swelling had been noticed by the mother about 2 months previously. The mother gave laxatives and when this measure

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Read at annual meeting, Southeastern Section of American Urological Association, Palm Beach, Fla. April 12–15, 1954.

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[2] MacCallum, W. G.: Textbook of Pathology. Philadelphia: W. B. Saunders Co., 1920.
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[5] Weisel, Wilson, Dockerty, M. B. and Priestley, J. T.: J. Urol., 50: 399, 1943.

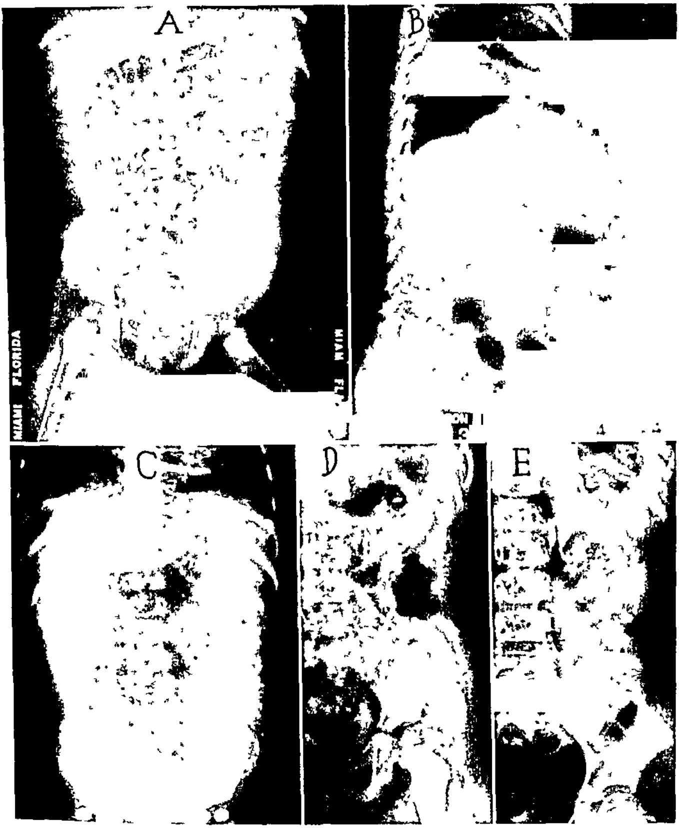

FIG. 2 *A*, original film showing circular area of calcification on left side *B*, original lateral film showing abdominal mass, forward displacement of bowel and calcified area apparently in midportion of mass *C*, original excretory urogram showing irregular, splotchy distribution of dye on right side and circular, calcified area in region of left kidney with marked blunting of calyces. *D*, postoperative, postirradiation excretory urogram. Wilms tumor on right side has been removed Note marked shrinkage of left calcified area and improved pyelographic pattern resulting from scattered irradiation of original tumor site. *E*, second postoperative excretory urogram (5 minutes) Five year interval since irradiation has again produced enlargement of calcified area

failed to reduce the abdominal swelling, x-rays were made which showed no trouble in the bowel. No gross hematuria or loss of weight had been noticed. Appetite was reported as fair. Examination disclosed a mass on the right side the size of an orange, apparently connected with the right kidney. There was questionable palpation of the spleen on the left side. Physical examination was not otherwise remarkable for a 14 months old baby girl. Excretory urography

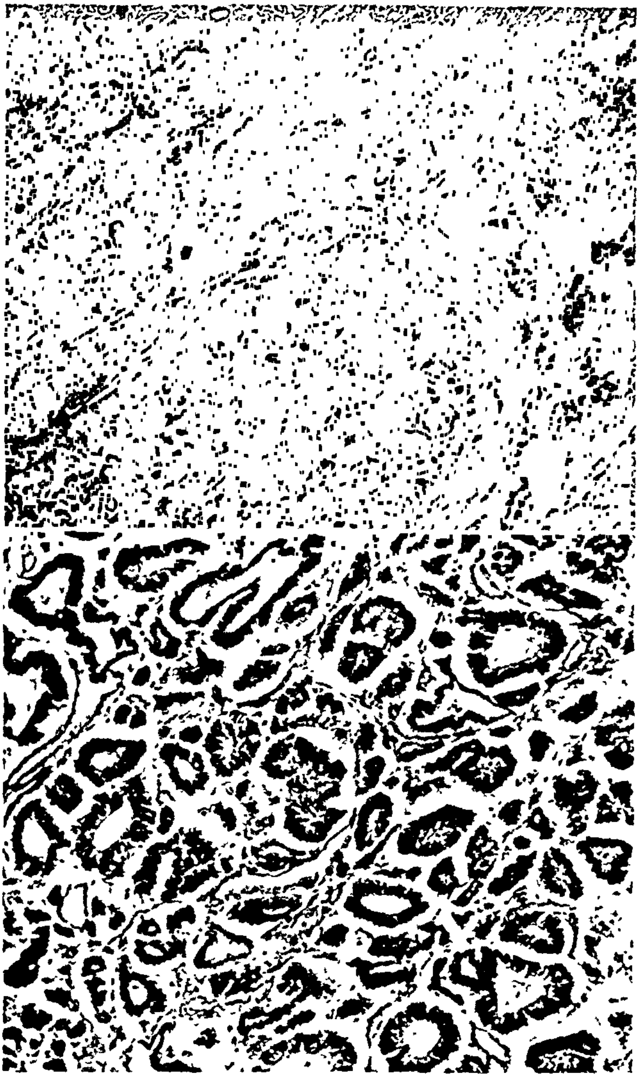

FIG. 3. *A*, first (right) tumor, low power. Predominance of glandular tissue of immature kidney epithelium. *B*, first (right) tumor, high power.

showed a tumor of the right kidney, presumably Wilms, and a calcified cyst of lower pole of the left kidney. A Wilms tumor was removed by nephrectomy from the right side 14 days after the patient was first seen; the preoperative diagnosis was right Wilms tumor; questionable solitary cyst on left side. Microscopic examination of sections taken from the tumor showed that it was completely separated from the capsule of the kidney. Though the tumor did not invade the kidney it was built up of immature kidney epithelium resembling a papillary carcinoma. A glandular papillary type was predominant. These belonged to the group of Wilms tumor. Diagnosis: Immature papillary carcinoma of the kidney. (Ph. R. Rezek, M. D.)

The patient was discharged from the hospital 8 days following operation. X-ray therapy was given, beginning 15 days postoperatively. Dosage was 2100 r. rt. ant. kid., 840 r. rt. post. kid. Following x-ray therapy, marked general improvement

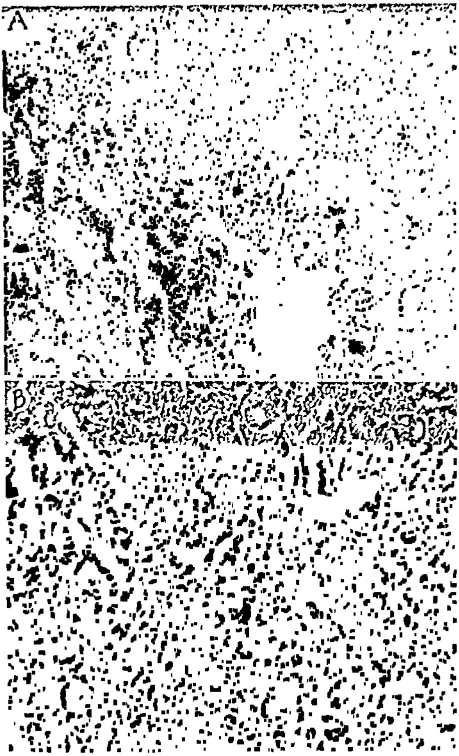

FIG. 4. *A*, second (left) tumor, low power. Predominance of undifferentiated tumor tissue with occasional area of adenocarcinoma. *B*, second (left) tumor, high power.

occurred: gain in weight, etc. Three months postoperatively the "cyst" in the left kidney was definitely smaller and less tender. Fourteen months after operation no tenderness in the left upper quadrant was elicited and the mass on the left side was not palpable. The weight was then 27¼ pounds. The urine was negative.

The patient was not seen again until January 1953, about five and one half years after the right nephrectomy. The weight was 51½ pounds, at age 7 years. However, the mass on the left side was again palpable and definitely enlarging. Urinalysis showed pH 6.0, specific gravity 1.012, albumin and sugar negative. There were 1 to 2 pus cells with an occasional clump per h.p.f. in the centrifuged specimen. The nonprotein nitrogen was 34.4 mg. per cent. The blood count showed 4.4 red blood cells, 12.2 gm. hemoglobin, segmented forms 45 and lymphocytes 40. Excretory urography disclosed progressive enlargement of the cyst on the left side. Not until 6 months later, however, did the mother consent to another operation. The patient re-entered the hospital in July 1953 and the operation was done under the mistaken diagnosis of "solitary cyst of the left kidney." A kidney tumor was found; it was impossible to separate it from the kidney itself, but the kidney was easily recognized and was relatively normal except at its lower portion, where the tumor was located. The tumor itself was of a fluctuant and cyst-like nature to a great extent. Biopsy of the more solid portion of the tumor was taken and the wound closed.

Microscopic examination of sections of the biopsy revealed the same tumor described in the right kidney in previous report of 1947. However, the biopsies not only showed papillary adenocarcinoma but also areas of extremely poorly differentiated tumor tissue. Diagnosis: Wilms tumor (Ph. R. Rezek, M. D.) (See figs. 2, 3, 4.).

A grave prognosis was given and the patient remained in the hospital for 5 weeks after the operation. Vigorous supportive treatment in the form of blood transfusions, high protein feeding and antibiotics was given. X-ray therapy over the left side (remaining kidney) was given: nineteen treatments were given between July 25 and August 18, 300 r. per treatment. Anterior, posterior and lateral ports were used. She was discharged from the hospital on August 27, 1953. Three months after discharge from the hospital the urine was negative except for 1–2 pus cells per h.p.f. (centrifuged). The mass in the left abdomen persisted. The child's weight was 46 pounds. Five months after operation the patient evidenced symptoms and findings of partial intestinal obstruction. She was given antibiotic therapy and on December 29, approximately 6 months after operation, a spontaneous fecal fistula developed in the center of the operative scar. From this point the patient's condition became progressively worse and she expired 7 months after the second operation. Autopsy was not obtained.

DISCUSSION

Family history. The father is aged 42, living and well. He had a kidney tumor removed in 1915 at age of 4 years. A personal communication from the Passavant Hospital in Jacksonville, Illinois states, "Unfortunately the records on this case were among those destroyed a few years back because they had deteriorated. I am told that in 1915 no pathological studies were done at this hospital. We do have the card in our index which shows that a boy by that name was operated on for removal of tumor of right kidney, including kidney, with final diagnosis given as 'tumor of right kidney.' "[6] There is no history of kidney tumor or cancer in the paternal grandparents of the patient being reported.

The mother, age 37, is living and well; no history of kidney trouble or cancer.

The child has 2 sisters. The older is 13 years old, living and well; no serious illnesses and no operations. The younger sister, aged 11 years, is living and well; she had a right kidney tumor removed, at age of 6 months, by Dr. Frank J. Pyle of Orlando, Florida. The pathological report on Dr. Pyles' case is as follows: "Microscopic: The tumor is formed by neoplastic tubules and more diffuse undifferentiated cells, all of which are hyperchromatic The neoplastic tubules are mostly small in size and atypical in shape Many possess a definite lumen, others are composed entirely of malignant cells In many places the tumor cells appear to blend in with the supporting stroma At some points the tumor is growing in the form of small cells almost spherical shaped which resemble lymphoid cells There are many areas of gross necrosis, some associated with calcium deposits What normal kidney tissue is present is compressed and atrophic Diagnosis Wilms tumor of right kidney "[7]

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[6] Ralph Bersell: Passavant Hospital, Jacksonville, Ill. Personal communication January 25, 1954.

The patient had no brothers

Bilateral occurrence Referring to Wilms tumors, Allen states that "primary bilateral involvement rarely occurs "[8] "Most cases of bilateral involvement have been found on postmortem examination "[9] The most recent available review by Sheach, in the *British Journal of Urology* in 1953,[10] includes a case added by him and enumerates 19 reported bilateral cases Apparently not included in this review are 4 cases of Gross and Neuhauser in 1949,[11] and a second case reported by Ladd in 1941 [12] Wilms collected 7 2 per cent bilateral tumors [13]

Family incidence This feature, in connection with Wilms tumors, is only occasionally referred to in the literature Familial tendency seems to be far less frequently encountered than bilateral involvement A search of the literature reveals only 5 reports of Wilms tumors in families

1) Walker in his analysis of 138 cases reported one in which a brother "was supposed to be similarly affected "[14]

2) A case is credited to Strumpel where 2 brothers were affected [15]

3) Deuticke had a case which was not operated on The patient had a 2½ year old brother who "died of the same condition "[16]

4) Three cases of Wilms tumor in one family were reported by Bobbio One case was proven, the diagnosis was clinical in the other two [17]

5) Maslow, along with a review, reported 4 cases, 2 brothers and 2 sisters in the same family, who had Wilms tumors Three of his 4 cases were proven by pathological study [15]

Comment Of the cases found in the literature exhibiting a familial tendency the references are mostly vague and unproven, some were not even operated on Only Maslow has reported more than one case in a family proven by pathological study We have found no reported case where progenitor and offspring have had childhood kidney tumors It is regrettable that no pathological studies were done on the father of our case and we must accept his diagnosis as clinical only, though he is the progenitor of two proven cases of Wilms tumor Furthermore, he has enjoyed a survival period of 38 years following the removal of a childhood kidney tumor.

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[8] Allen, A C The Kidney Medical and Surgical Diseases New York Grune and Stratton 1951

[9] [illegible]

1950

1858 1941

Dean, A L and Pack G T J A M A , 98 10, 1932

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Calcification in Wilms tumors receives only incidental mention in the literature and in textbooks on pathology. No doubt it follows the established pathological principle of deposition of minerals in diseased or necrotic tissue or in tissue areas of poor blood supply. In our case, however, it was sufficiently extensive to enable us to follow by x-ray films the variations in size of the second tumor. Scattered irradiation from treatment of the first tumor site produced a marked shrinking of the calcified area and a great improvement in the pyelographic pattern. The last urinalysis obtained on our patient, 4 months following x-ray therapy over the remaining kidney, showed 1 plus albumin and abundant hyaline and fine granular casts, evidence of radiation nephritis the fundamental pathology of which is sclerosis of the blood vessels of the kidney.[18]

CONCLUSION

A case of bilateral Wilms tumor occuring in a Wilms tumor family, and exhibiting other remarkable features, is presented.

422 Ingraham Bldg., Miami 32, Fla.

[18] W. A. D. Anderson. Personal communication, 1954.

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RENAL AND URETERAL SURGERY WITHOUT INTUBATION

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Observations made during the past 3 years tend to confirm a suspicion, held earlier, that the use of splinting tubes or catheters is not always necessary and indeed, their use actually may be harmful The nephrostomy tube is included in this category only when it is used as an adjunct to renal surgery Nephrostomy, on the other hand, when used as an operation to relieve urinary obstruction, is a different matter and remains a valuable procedure The terms 'tubes' and 'catheters' are used here in their broadest possible meaning, in an attempt to cover all modifications that have been designed for various purposes

More specifically, evidence both clinical and experimental will be presented to indicate that the splinting and nephrostomy tubes may be eliminated in four types of operations 1) Y plastics on ureteropelvic juncture, 2) in heminephrectomy or calycectomy the nephrostomy tube can be eliminated, 3) ureterovesical re-implantation may be done without a splinting catheter, 4) constricted areas in the ureter may be simply incised and allowed to heal with satisfactory results, without benefit of any suturing, intubation or nephrostomy

Elimination of splinting and nephrostomy tubes in connection with Y plasty of the renal pelvis had its inception when it was observed, on the occasional patient, that if the tubes inadvertently came out results seemed to be as good and healing proceeded rapidly

In the first few patients only the splinting tube was eliminated The nephrostomy tube was retained, but later it was eliminated as well and drainage was provided by an opening in the renal pelvis

The protagonists of the tube have advocated its use to prevent obstruction from developing at the ureteropelvic juncture Obstruction probably develops from two principal causes The first is due to a kinking of the ureter at this point Occasionally an S shaped deformity results from a redundancy of the ureter The kidney, having been mobilized and consequently freed from its normal attachments to the perirenal fat, tends to occupy a lower position when replaced, resulting in redundancy of the upper ureter This objectionable feature can be eliminated by placing the kidney high in the fossa and supporting it by nephropexy The second cause of obstructions at this point is faulty repair of the apex of the plastic V shaped piece of renal pelvis as it is sutured into the ureteropelvic juncture We find that excessive suturing increases the tendency to fibrosis Only a minimal number of fine chromic catgut stitches are used No attempt is made to obtain a watertight closure

Drainage in the absence of the nephrostomy tube is provided by either leaving a space of 1½ cm unsutured in the renal pelvis or making a stab opening at another site

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Read at annual meeting, American Association of Genito Urinary Surgeons, Shawnee on Delaware, Pa May 26–28, 1954

In those patients who require heminephrectomy or calycectomy, a nephrostomy tube has been eliminated; instead, a slash 1½ cm. long is made in the renal pelvis providing for free drainage and egress for blood clots. Experience suggests that not only do nephrostomy tubes encourage the introduction of infection into the kidney, but they may be the cause of hemorrhage. Elimination of the tube is not positive assurance that hemorrhage will be avoided, but since we have stopped inserting it, severe bleeding has not been observed.

Re-implantation of the ureter into the bladder may be done safely without a splinting ureteral catheter. A careful mucosa-to-mucosa anastomosis without tension is all that is required. A rubber tissue drain placed behind the bladder and a suprapubic tube in the bladder will suffice. The fundamental principle appears to be the same as in the anastomosis of ureter to bowel, where splinting catheters are not in general use.

In the fourth group, those patients who have undergone ureterotomy without intubation, the indication for the operation is a constricted area in the ureter that is either so extensive or situated so far below the ureteropelvic juncture that Y plasty is impractical.

The technique consists of a linear incision in the ureter for a sufficient length to include all of the constricted area. Following incision the ureter appears to roll back forming a flat ribbon-like structure; no effort is made to repair it by suture or the introduction of any splinting tube or catheter. Adequate drainage is provided by ordinary rubber tissue.

RESULTS

These principles have been used in 20 cases. All the operations were done during the past 3 years by members of the resident and attending staff, at the Brooklyn Hospital and the Veterans Hospital. The cases may be divided into the following groups:

	cases
Y plastics on renal pelvis (one on solitary kidney)	4
Heminephrectomy (calycectomy)	5
Ureterovesical anastomosis	2
Ureterotomy without intubation (two on solitary kidneys)	9

Figures 1 and 2 depict 2 cases of ureterotomy without intubation.

No deaths occurred in our series and nephrectomy has not been required for any purpose. No stones formed in any patients during what might be called the convalescent period. One patient, Mrs. B. (Brooklyn Hospital No. 128,856), "a chronic stone former," who underwent bilateral calycectomy for calculi in both kidneys, began to reform a calculus in the left kidney 1 year after operation. All patients except one are free of infection. Convalescence is rapid following the plastic operation on the renal pelves and ureterotomy. Urinary drainage in most instances was absent before the fifth day and did not persist beyond the fourteenth day, except in the patient on whom ureterovesical re-implantation was done; in that instance 25 days were required for complete healing. All patients

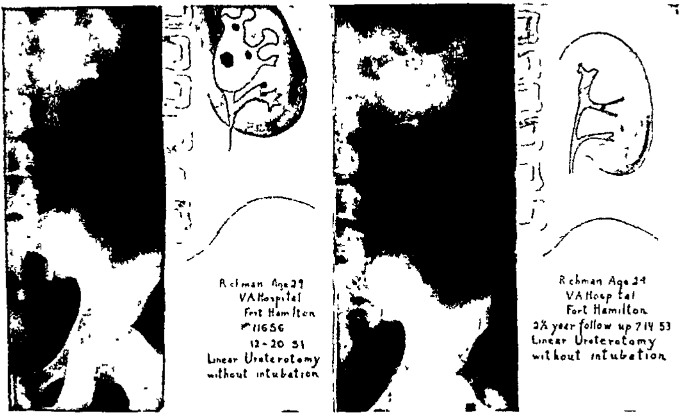

FIG 1. Two and one-half year follow-up on extensive linear ureterotomy performed on upper third of ureter without intubation. Preoperative film on left.

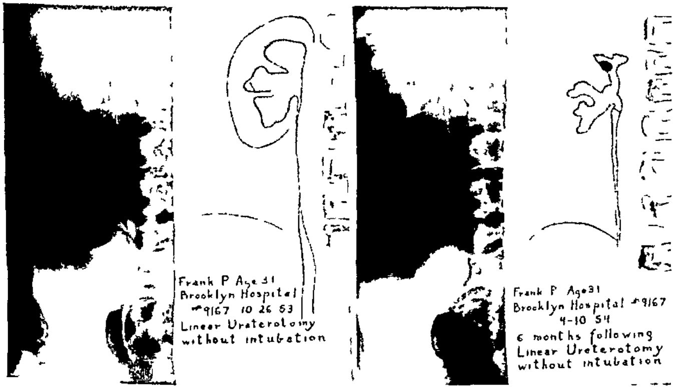

FIG. 2 Extensive linear ureterotomy in upper third of right ureter. On right is shown postoperative result 6 months later.

who underwent heminephrectomy were discharged on the fourteenth postoperative day.

Results of plastic operations on the renal pelvis and ureterotomies are considered uniformly good as judged by short hospital stay, relief of symptoms, and absence of infection and obstruction. Nineteen of the 20 cases are free of infection.

Two patients were subjected to ureterovesical re-implantation. The first one, a man with stricture at the intramural portion of the ureter, A. S. (Brooklyn Hospital No. 144,118) obtained a good result. A second case, W. M. (Brooklyn Hospital No. 87.242) had a neoplasm of low grade that involved the intramural ureter. Following resection the ureter was found to be too short for re-implantation, and it was necessary to construct a tube of bladder to supplement the shortened ureter. A constriction resulted and about three months later, a cutaneous ureterostomy was necessary. I believe that this obstruction resulted from tension at the site of anastomosis rather than the absence of a splinting tube. Nevertheless, the case is considered a failure.

DISCUSSION

The drainage tube or catheter is one of our oldest and most valued instruments, but its use has been developed and extended far beyond its true scope. Excessive application of a valued precept is not new; one need only recall the extended use of the theory of 'focus of infection', a theory that was applied in the 1930's to include such diverse processes as duodenal ulcer and rheumatoid arthritis.

The drainage tube has already passed its high water mark and one detects a recession in its use. Its use in the management of the patient with prostatic obstruction has been greatly reduced. (There was a period in which all prostatics were prepared for surgery by catheter drainage.) Occasionally from various quarters was heard the uncertain theory that the introduction of infection into the urinary tract was actually beneficial as the patient thereby acquired an immunity. Plastic procedures on the urethra are not usually attempted with the catheter as a splint nor are tubes used in uretero-intestinal anastomosis. Clinical experience with intubation has been varied. Higgins,[1] discussing Davis's paper at the meeting of the American Urological Association in Buffalo in 1947, reported two instances of stricture following the use of intubation, following ureterotomy. He also stressed the importance of keeping the surgical technique as simple as possible. Henline,[2] discussing the same paper, states, "The greatest hazard to prolonged nephrostomy or pyelotomy drainage with splinting of the ureter is the tendency to the formation of renal calculi." Henline reported 45 patients operated on by this method in whom the tubes had been allowed to remain in situ for 6 weeks, and of these, calculi had developed in 11 per cent.

Considerable experimental evidence is also available to indicate that the splinting tubes are unsuccessful in the laboratory animal. Trautner and Raaschou[3] recently reported their experiences on the regeneration of the ureter in dogs after intubated ureterotomy. No complications developed in only two of the 9 ureterotomies done on 7 dogs; in six, varying degrees of hydronephrosis occurred. In dog No. 6 a postmortem examination on the fiftieth postoperative day disclosed a severe inflammatory stricture at the site of resection and severe pyonephrosis and purulent peritonitis. Among other complications, ossification at the site of resection in 2 animals is mentioned, slight hypertension in 2 cases, both combined with hydronephrosis, and reflex anuria in 1 case followed by death of the animal. In summary he states, "Altogether complications have been so numerous that we would not have found it safe on the basis of the foregoing experiments to apply the method of intubation on patients suffering from

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[1] Higgins, C. C.: J. Urol., 59: 860, 1948.

[2] Henline, R. C.: J. Urol., 59: 860, 1948.

[3] Trautner, K. and Raaschou, F.: J. Urol., **71**: 274, 1954.

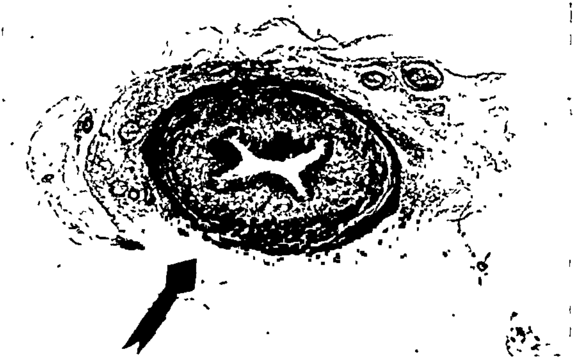

FIG. 3. Dog No. 474. Weight 18 kg. On January 20, 1954 linear incision 3 cm. long was made in upper third of left ureter. Nephro-ureterectomy February 10, 1954. Photomicrograph represents transverse section through previously incised ureter. Healing is complete without evidence of scar or any reduction in size of lumen. Arrow points to break in muscularis, possibly site of incision.

ureteral strictures; however previous experience from clinical surgery shows that such complications may be ascribed to specific conditions in the technique applied and that they are very seldom met with in patients."

In 1948, Davis, Strong and Drake[4] studied regeneration of the ureter in 6 dogs using the technique of intubation, but the corresponding kidney was removed in each instance at the time of intubation. It seems that regeneration of the ureter is of no great consequence if the integrity of the kidney is not preserved.

In 1950 Kimbrough et al.[5] made similar experiments on 4 dogs. Three of the four sustained damage to the kidney following ureterotomy with the use of the splinting tube. In one animal the kidney was completely destroyed and calculi were found in both the kidney and bladder; in the second dog a dense stricture of the ureteropelvic juncture was found with severe hydronephrosis above. The third had hydronephrosis and hydro-ureter of moderate degree.

We have subjected 4 dogs to ureterotomy without the use of any splinting or nephrostomy tube. Drainage was provided by rubber tissue, passed down to the site of incision into the ureter. The kidneys in all dogs appeared normal on gross inspection at the first operation. They were allowed to remain in their normal position until the end of the experiment or until the death of the animal. The dogs were of medium size, weighing from 13–18 kg. All operative procedures were performed under barbiturate anesthesia. The results were briefly as follows:

Dog 1 (lab. No. 474): On January 20, 1954, a linear incision 3 cm. long was made in the upper ureter, involving the ureteropelvic juncture. None of the ureter was removed in this animal. Urinary drainage could not be detected after the fifth postoperative day. On February 10, 1954 the kidney and ureter were

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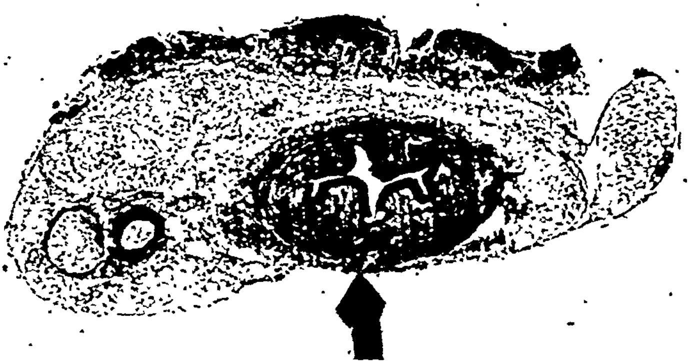

FIG. 4. Dog No. 554. Weight 19 kg. March 3, 1954, section estimated at one-third to one-half of wall resected from left ureter. Wound closed with drainage. No sutures or splinting tubes used. March 24, 1954, ureter removed for microscopic study. Arrow points to possible site of previous resection. Lumen was reduced but adequate. No evidence of stricture or obstruction.

removed. The urine was clear, the kidney was normal; no evidence of hydronephrosis was seen and the ureter had healed without evidence of fibrosis or reduction in size of the lumen. The result was so good we could hardly believe that the proper level had been sectioned (fig. 3).

Dog 2 (lab No. 415): On February 3, 1954 a linear incision 3 cm. long was made in the left upper ureter; no sutures or a splinting tube were used. The wound was dry on the fifth postoperative day. On February 17, 1954 a left nephroureterectomy was done. Healing was the same as described in dog 1.

In the remaining 2 dogs (Nos. 554 and 583) resection in the upper third of the ureter was done on one side. Between one-third and one-half of the ureteral wall was resected for a distance of 3 cm.; no suturing or tubes were used as splints—only a rubber tissue drain was inserted.

Urinary drainage was continued for a longer time in these dogs, a period of 14 days. Both dogs survived and 3 weeks later the kidney and ureter were removed for examination. The ureters on section were found to have a slightly reduced caliber, but the wall had regenerated producing an adequate lumen; no infection or hydronephrosis was observed (fig. 4).

SUMMARY AND CONCLUSIONS

Clinical evidence indicates that surgery of the kidney and renal pelvis may be successfully done without the use of splinting or nephrostomy tubes. Adequate drainage can be provided by leaving a vent in the renal pelvis. Ureterotomy may be accomplished by making a linear incision through the strictured area. Healing by primary intention with adequate caliber results.

Elimination of these adjuvants reduces renal and ureter surgery to its simplest possible level and produces satisfactory results from the standpoint of 1) short period of postoperative hospitalization, 2) relative absence of infection, 3) relief of obstruction and 4) preservation of renal function.

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THE ELASTIC PROPERTIES OF NORMAL URETER

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Physiologic demands upon the ureter extend beyond passive conduction of urine from kidney to bladder While the characteristics of ureteral tone, peristalsis, and innervation derangements have been extensively studied, the functional significance of ureteral elasticity has not been investigated We are aware of the role played by blood vessel elasticity in hemodynamics, but the place of elasticity in ureteral physiology is not clear This study was designed to evaluate the normal range of ureteral elasticity and correlate the physical characteristics with the microscopic structure

METHOD

Elastometer Five to seven cm segments of normal ureter were obtained either at time of nephrectomy or within less than four hours post mortem A small portion was used for microscopic examination and the remainder for elasticity evaluation

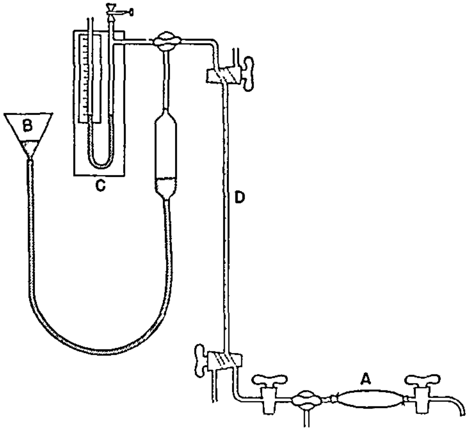

FIG 1 Elastometer After Hallock and Benson[1]

The elastometer devised by Hallock and Benson[1] for studies of aortic elasticity was modified to accommodate segments of ureter (fig 1) This equipment makes possible the simultaneous estimation of volume and pressure within an isolated segment of ureter Pressure within the ureter (*A*) is adjusted by elevating or lowering the mercury reservoir (*B*) The manometer (*C*) reflects changes in

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Read at annual meeting Southeastern Section of American Urological Association, Palm Beach, Fla April 12-15, 1954

[1] Hallock, P and Benson J C Studies on elastic properties of human isolated aorta J Clin Investig , **16** 595, 1937

TABLE 1. *Elastic tissue in ureters*

Age, Sex, Race	Submucosa	Muscle	Adventitia
Stb. WM	+	+	+
6 wks. CF	0	0	+
6 mos. WM	±	±	+
14 mos. WM	+	+	+
2 WM	0	0	+
9 WM	±	±	+
13 CM	+	+	+
17 WF	0	+	+
18 WM	+	+	+
20 WF	+	+	+
22 WM	+	±	++
22 WM	0	±	0
23 CM	±	±	±
24 WM	+	+	+
27 WF	0	0	0
27 WF	±	0	±
31 WF	+	+	++
31 CM	0	0	+
34 CM	+	+	+
35 WM	+	+	±
36 WM	+	+	+
36 CM	0	0	+
37 CM	+	+	±
39 CF	+	+	+
40 CF	+	+	+++
40 WM	++	±	+
44 WM	±	±	+
45 WM	+	+	++
46 WM	+	+	+
46 WM	+	+	+
48 WM	±	±	+
48 CF	+	+	++
49 CF	+	++	++++
50 WM	++	+	+
51 WM	+	+	±
51 WF	+	+	+
51 CM	+	+	±
52 WF	±	±	+
54 WM	+	+	+
57 WF	++	+	++
59 WF	±	+	++
60 WM	+++	++	+
62 WM	±	±	+
63 WM	+	+	+
64 WF	+	+	+
65 CM	++	+	+
66 WM	±	±	+
69 CM	±	+	+
70 WM	±	±	+
71 WM	±	±	+
78 WF	+	+	+

pressure while the 10 ml. burette (*D*) indicates volume variation. The capacity of the ureteral segment is first measured at a standard pressure of 10 mm. Hg. The intra-ureteral pressure is then increased by 20 mm. Hg steps, measuring volume at each pressure. The data obtained are plotted graphically with pressure along the abscissa against the corresponding percentage increase in volume along the ordinate. In this way a simultaneous estimate of both circumferential and longitudinal relative elasticity is obtained. At the conclusion of each experiment the pressure is returned to the 10 mm. standard to make certain that the elastic limit of the ureter has not been exceeded.

HISTOPATHOLOGY

The ureters of fifty-one individuals without urologic disease were fixed in Kaiserling solutions. Cross sections and longitudinal sections were taken of one ureter from each individual Consecutive sections of each block were stained with hematoxylin and eosin, Masson's trichrome, Verhoeff-van Gieson and Weigert's elastic tissue with van Gieson counterstain techniques. Each slide was examined microscopically, and a value of from 0 to 4 plus was placed on the relative number of elastic fibers in the submucosa, muscle and adventitial layers of each ureter. These values are tabulated in table 1. A ± value means that only a few equivocal fibers were seen.

OBSERVATIONS

Elastometer. To clearly demonstrate age variants the specimens were divided into two groups. Group 1 includes ages 20 years through 40 years and group 2 represents specimens from patients over 60 years of age. A 20-year hiatus

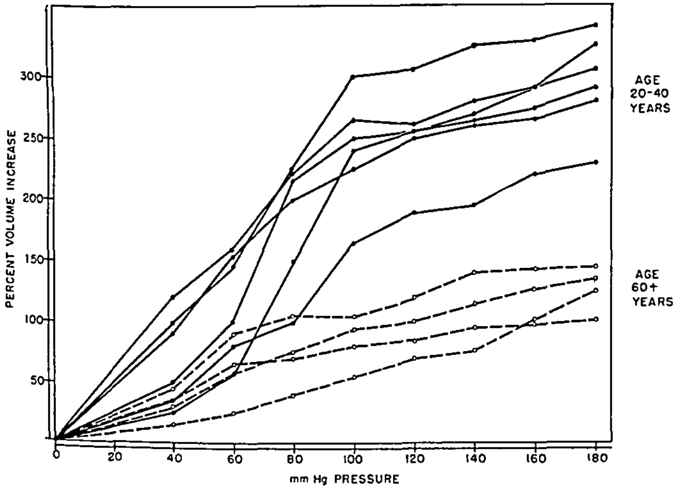

FIG. 2. Age variation of ureteral elasticity

separates the two groups to minimize overlapping data. The volume-pressure ratio data are graphically summarized in figure 2.

The elastic limit of the ureters in the young age groups was not passed at 200 mm. Hg pressure. This same pressure, however, exceeded the range of reversible extensibility in two of the specimens from older persons.

Histopathology. The concentration of elastic fibers varied directly with the density and amount of collagen present in any area. In instances where a definite thick layer of collagen was present, elastic fibers were found in greatest number and forms. Spirals of elastic tissue may occur in the most dense collections of collagen, although the usual form of the elastic tissue was a wavy fiber. Definite layers of collagen may occur in the adventitia and in the submucosa or tunica propria (fig. 3). In some instances, such a layer formed a complete cylinder of connective tissue in the ureter. More frequently the layer was only partial, or consisted of elongated or spherical masses of collagen that contained elastic

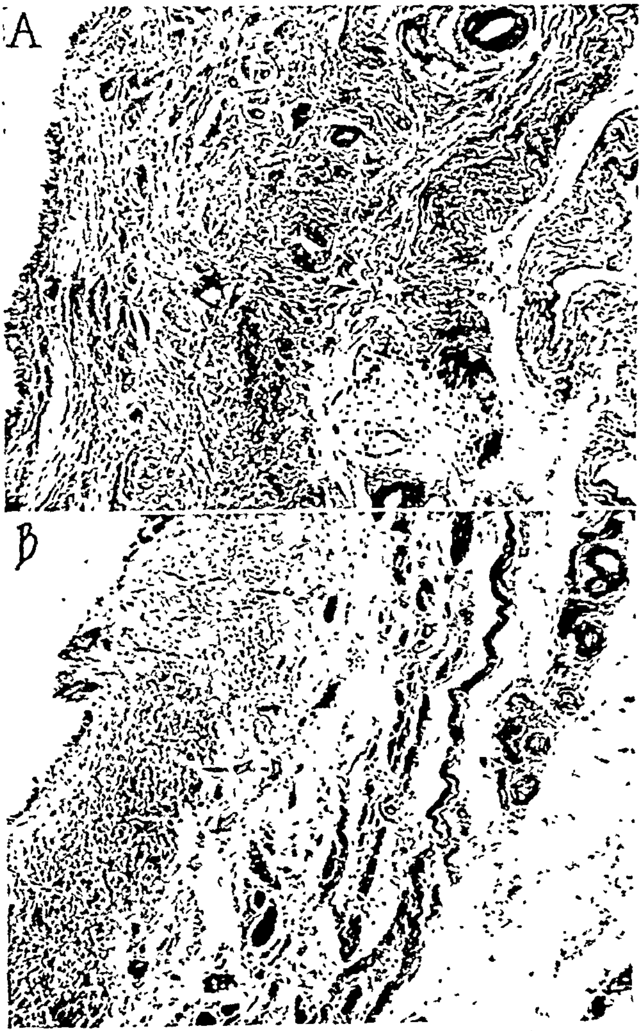

FIG. 3. *A*, dense layer of elastic tissue in adventitia. Mucosa is at extreme left. *B*, dense layer of elastic tissue in submucosa. Mucosa is at extreme left. Verhoeff-van Gieson stain.

fibers Other collagen fibers were scattered loosely in the adventitia, muscularis and tunica propria with occasional elastic fibers The elastic fibers may be absent

Many different diseases caused the death of these individuals However, each ureter appeared to be normal grossly and microscopically.

Artefacts which could contribute to the interpretation of the histologic preparations of the ureters have been considered, such as the length of time from death to fixation of the ureters and the length of time the ureters had remained in a fixative Evaluation of 3 cases in which fixation was initiated at forty or more hours after death leads us to conclude that autolysis for periods longer than 30 hours may affect the elastic fibers and reduce their number in microscopic preparations

DISCUSSION

The elastometer data reveal a definite diminution in elasticity with age Ureters from persons below the age of 40 years show a percentile capacity increase almost double that of the older group Both groups exhibit a distensibility limit beyond which pressure increases produce relatively little volumetric change so that the terminal portions of the curves tend to flatten.

Histologic data on elastic fibers in ureters are conflicting It has proved difficult to find adequate descriptions of the elastic tissue in the ureters The standard texts mention dense layers of elastic tissue in the tunica propria, but a glance at table 1 will show that this finding is by no means constant Sometimes elastic tissue cannot be found in the tunica propria There is great variation in the amount and arrangement of elastic fibers so that it is improbable that the elastic tissue alone accounts for the variations in elasticity with age The element which varies with age may be smooth muscle

These findings may be of clinical importance in that the ureter is normally empty, its lumen obliterated by close approximation of the walls In this normal state there is considerable resistance to transmission of obstructive back pressure to the kidney Such back pressure may be more readily transmitted up a ureter that is beginning to lose its tone and elasticity Thus this protective buffering mechanism may be adversely affected by age Of further possible significance is the observation that relatively high intraluminal pressures of short duration did not exceed the elastic limit of the ureters from young persons Two specimens from the older age group, however, were less resilient and remained partially dilated

SUMMARY

Ureteral tissue acts as a biologic elastometer

The histologic characteristics of ureteral elastic tissue have been described

Ureteral elasticity diminishes with age, but elastic fibers alone do not account for this change

There is no correlation between age, sex or race and the amount of elastic tissue identified by histologic techniques

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USE OF ANTISPASMODICS IN TREATMENT OF SPASTIC URETERITIS

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The purpose of this paper is to report our experiences with the use of antispasmodics as an adjunct to the surgical treatment of spastic ureteritis. The individual techniques used are not new. Our methods of handling the cases, however, differ to some extent from those used in any other clinic with which we are familiar.

The pathology of the ureter cannot be thoroughly discussed without bringing up the monumental work done by Guy Hunner. These findings have been and still are the subject of some controversy. Dr. Thomas D. Moore has also contributed a great deal to our knowledge of this subject.

We expect to deal with spastic ureteritis in this paper exclusively and will not take up any other process in the ureter.

First, we wish to give you our criteria for establishing a diagnosis of spastic ureteritis.

1) The pain may be either of the colicky-type referred to the characteristic site of renal colic or it may be dull in nature and frequently described by the patient as a type of pain which gives one the desire to relieve it by squeezing, as in the case of a small furuncle or similar lesion.

2) X-ray studies do not show spastic ureteritis but serial pyelograms are thought by some to be advantageous.

3) One must be able to palpate the site of the lesion by means of the withdrawal bulb technique, as advocated and demonstrated by Hunner.

Many lesions, both in the urinary tract and extra-urinary, can cause this type of pain. Thorough studies of the urinary tract as well as the adjacent structures are necessary to rule out the possibilities of other lesions than spasticity of the ureter. In approximately ten per cent of the cases of patients referred to us with renal colic, both male and female, the final diagnosis is "spastic ureteritis." Frequently a tentative diagnosis is proved incorrect by the discovery of adjacent pathological processes. There is a distinct possibility that the spasticity in the ureter is set up definitely by the adjacent disease. The most common extrarenal causes in our cases are pelvic disease in the female, prostatic and seminal vesicular disturbances in the male, diverticulitis of the colon in both sexes, and arthritic pain. The most frequent types of disease within the urinary tract causing confusion are ureteral calculi which do not visualize on x-ray, fibrous strictures of the ureter, and kinks of the ureter. One should also never forget that definite hypertrophy of the longitudinal fibers in the lower ureter occurs during pregnancy and causes definite back pressure on the upper ureter and kidney. This process is, for the most part, demonstrable in x-rays.

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The clinical and laboratory studies were made possible by a grant from the William P. Poythress and Company, Richmond, Va.

In our hands, the value of x-ray in the diagnosis of spastic ureteritis is the fact that the film does not show any abnormality in contradistinction to definitely demonstrated fibrous strictures in cases of hypertrophy and dilatation of the ureter above the site of stricture. We agree that a large series of serial uretero-pyelograms might possibly disclose useful information, but in our hands this particular field has not been productive.

Our most frequent error in diagnosis is failure to recognize a small calculus that is not palpable by the ureteral catheter or to the bulb on its withdrawal, and which does not show on x-ray or cast such a small shadow that it is overlooked, particularly in the wet film. We should like to caution against reading films too rapidly, particularly when wet, and we believe that all cases of spastic ureteritis should have minute examinations of the pyelo-ureterograms at the site of the spasticity to rule out small calculi in which diagnosis is difficult. Our clinic is located in an area in which urinary calculi are common. We see a great many such cases each year, and a definite percentage of the small ones are not diagnosed; and, at times, some embarrassment results, particularly when the patient expels the calculus following instrumentation.

The keystone of the arch which supports the diagnosis of spastic ureteritis is the ability to demonstrate a hang to a bulb of a ureteral catheter which has been passed above the site of the spasticity and withdrawn through the spasticity. This was first demonstrated by Hunner. The proper technique for this surgical maneuver is extremely exacting, both as to tactile ability and dexterity on the part of the surgeon and exactness of the equipment. It is our opinion that only the open end endoscope type of instrument is completely satisfactory for this delicate diagnostic procedure. The McCarthy panendoscope is the instrument of choice in our clinic. Although we personally are not experts in the use of the Kelly open end endoscope, we have used it and believe that ureteral strictures and spastic ureteritis can be diagnosed nicely by those expert in using that instrument. We have not found that the recumbent position, water distention of the bladder, or sodium pentothal anesthesia interferes with our ability to make the diagnosis. The McCarthy panendoscope must have no obstruction and we personally prefer not using a guide when this diagnostic procedure is attempted. The guide has a tendency at times to cause a false sense of hang when the bulb is being withdrawn.

We have used all the types of bulbs, including handmade wax bulbs first demonstrated and advocated by Hunner, the bulbs constructed as a part of the woven ureteral catheter, and the bulbs introduced by Walther and Willoughby of New Orleans. In our hands the most satisfactory is the metal Walther bulb with the 3 inch 3F filiform preceding it. We first use an 7F bulb and rarely go higher than an 12F bulb for diagnosis or treatment. We hereby acknowledge the possibility that we may be missing some of the large caliber spasticites by not using larger bulbs and we do occasionally use one when all other diagnostic possibilities have been exhausted. We want to again stress the desirability of extreme gentleness in this maneuver. A roughly passed bulb will do great harm besides making the procedure practically valueless as a diagnostic procedure.

We believe that considerable care and definite technical skill as well as experience are necessary to make a diagnosis of spastic ureteritis. We do, however, feel that the time and effort are justified when we review the number of patients relieved who have had failures in treatment, both at our hands and by others, and relieved when their cases were exhaustively studied.

After the diagnosis of spastic ureteritis has been made, the next problem is therapy. We have retrenched considerably in our opinion of dilatation of the ureter during the past few years. The senior author recalls vividly a case about twenty-four years ago in which he made the diagnosis of ureteral stricture; at that time we did not separate ureteral stricture from spastic ureteritis; and the patient was dilated up to a 10 bulb. The patient was improved but was not relieved for any length of time and, after becoming discouraged, decided to consult Dr. Hunner. He dilated the patient's ureter, using bulbs which would not pass though an 24F panendoscope, and she obtained complete relief.

As a result, we had additional sheaths made for our panendoscopes up to size 32F. For some years it was our custom to dilate these ureters at weekly intervals to large diameters, using care not to traumatize the tissue and passing the same bulb gently until the next size could be introduced. This procedure was time-consuming and expensive, and many patients refused to complete the treatments. Even with the advent of sodium pentothal, the problem was still acute. The pain at the time of the cystoscopy was eliminated, but the postoperative reaction and the number of cystoscopies still remained the main reasons for not completing the necessary treatments. We began casting about for something different. We noted that in those cases of violent reactions following dilatation of the ureter, particularly those that had some minor bleeding and in which we re-inserted ureteral catheters to permit free drainage and relieve the pain of back pressure, the patient did not require repeated cystoscopies or the passage of the larger bulbs for relief. We finally worked out a technique that yielded the same result that we formerly obtained by a long series of ureteral dilatations and the use of larger bulbs. We used smaller bulbs, in most cases not higher than 10F, then left a ureteral catheter in situ for 24 hours.

Following conversation with Dr. McDonald of Atlanta, who also uses ureteral catheters left in position for dilatation of the ureter, we began to shorten the time in which the catheters were left in position. We now believe that a period of 6 hours will give just about as good a result as one gets from longer periods, plus the fact that less vesical and ureteral irritation are produced. We now habitually dilate the ureter gradually to 10F, starting usually with a 7F bulb. After each dilatation, we strap in position, in the ureter, a 6F ureteral catheter and tie it to a self-retaining 5 cc 18F Foley bag catheter. An average of two to three dilatations are all that are now required as against our old average of eight to ten dilatations.

It was at this time that we directed our attention to the value of antispasmodics as adjuncts to the treatment of spastic ureteritis. Tincture of belladonna was discarded early due to its side effects and we began trying various synthetic antispasmodics. We finally found three that were more satisfactory in our hands than others: adiphenine hydrochloride (trasentine), isomethepten, methylisooctenylamine, mucate (octin), and beta-diethylaminoethyl diphenylthioacetate (trocinate). To avoid the very long chemical names, from now on we will refer to these synthetic drugs by their common names.

It shortly became evident that the individual drugs had certain advantages. Apparently octin exerted a more favorable influence in our cases of ureteral colic due to blood clot or to calculus in the ureter than the other antispasmodics. Trasentin apparently had slight advantage over the other drugs in the control of associated gastro-intestinal spasm; but the third synthetic, trocinate, apparently worked better in our cases of spastic ureteritis. After some trial, we took up the matter with its manufacturers and secured a grant for an extensive clinical trial and also laboratory experimental work in an effort to determine the reason for our clinical findings.

After an experience of more than 2 years, we believe that beta diethylaminoethyl diphenylthioacetate is the drug of choice when used in conjunction with the technique which we have delineated in the treatment of spastic ureteritis. We are satisfied that the use of this antispasmodic has shortened the course of treatment necessary and has made the patient more comfortable. A single follow-up dilatation often will clear up a reccurrence of symptoms after the patient has been free for a number of months if it is re-inforced with a week or ten days' treatment of the drug. Our clinical findings do not show any value of the addition of phenobarbital to the plain drug except in patients who show a definite indication for phenobarbital as well.

Laboratory studies on excised rat and rabbit tissue have been carried out in connection with this present clinical study of antispasmodics in spastic ureteritis

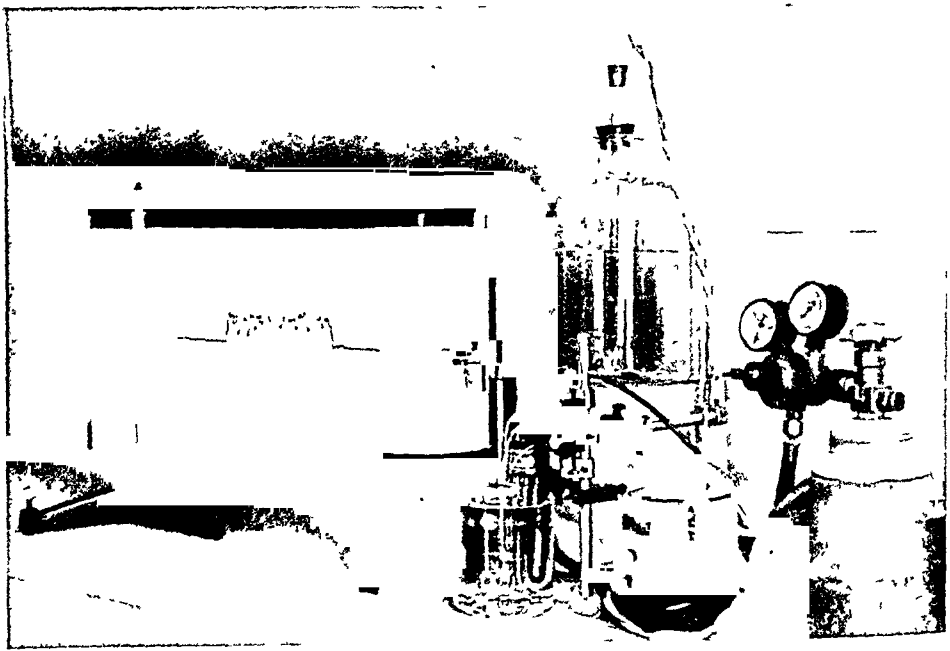

FIG. 1

These pharmacologic studies compare the effects of the synthetic antispasmodics and anticholinergic drugs against spasms caused by acetylcholine bromide and barium chloride.

Both Burger and Sollman in their research work feel that acetylcholine bromide reproduces in susceptible excised muscle the identical spasm caused by excessive activity of the parasympathetic nervous system upon the same muscle in the intact body. In fact, acetylcholine is stated by these investigators to be the chemical which is rapidly synthesized from the inactive choline near the parasympathetic nerve-endings and which actually causes the smooth muscle contractions resulting from parasympathetic nerve impulses (neurogenic contractions or spasms).

Barium chloride reproduces in susceptible excised muscle tissue a spasm which simulates a spasm of the actual muscle occurring in the intact animal and irrespective of innervation (a myogenic or intrinsic smooth muscle spasm).

Figure 1 shows the rather simple apparatus with which the muscle studies were made. The excised muscle strip is suspended in an oxygenated Locke-Ringer solution maintained at constant temperature (37C) by a thermo-regulator The contraction and relaxation of the muscle, as brought about by additions of stimulating and antispasmodic drugs to the Locke-Ringer bath, are transcribed by the muscle kymograph, as shown.

Figure 2 reveals an interesting and significant difference in the response of ileum tissue and ureteral tissue of the rat and rabbit to the stimulating effects of barium chloride and acetylcholine bromide The ileum from the rat and from the rabbit is stimulated into spasm by a 1:10,000 concentration of barium chloride The ureters of the rat and of the rabbit are similarly though slightly less responsive to barium chloride, being stimulated into spasm by a 1:5,000 concentration of barium chloride

The response of the ileum and ureteral tissue to the stimulating effects of acetylcholine bromide is entirely different. The ileum of the rat and of the rabbit is stimulated into an intense spasm by the addition of a 1:1,000,000 concentration of acetylcholine bromide. The ureters of the rat and rabbit are, on the other

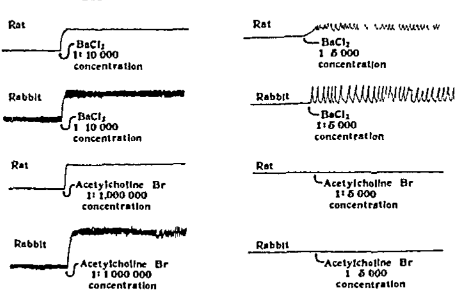

FIG 2 Effect of stimulating drugs on isolated ileum and ureter of rat and rabbit suspended in Locke Ringer solution at 37C.

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Laboratory studies on excised rat and connection with this present clinical stud

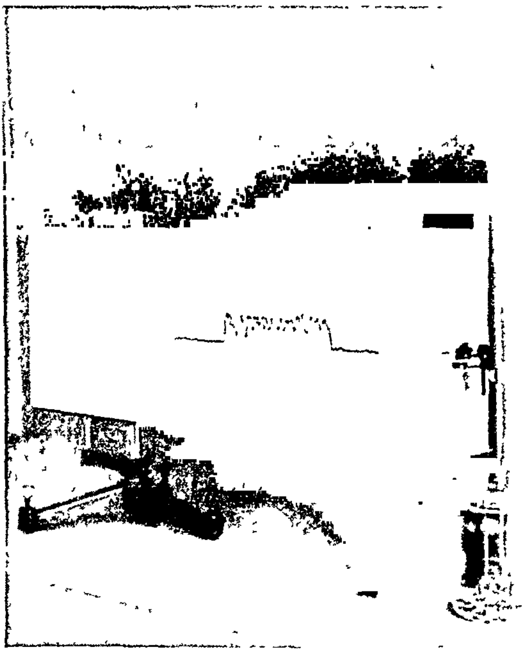

FIG. 1

The tracings reveal that trocinate will relax a barium chloride spasm of the rat ureter in 1:100,000 concentration while trasentine and octin, other antispasmodic drugs, were effective only in a concentration of 1:25,000. Several anticholinergic drugs were similarly tested. A 1:20,000 concentration of bentyl only moderately reduced a barium chloride spasm, a 1:25,000 concentration of pro-banthine was required to relax a barium chloride stimulated rat ureter, and a 1:16,600 concentration of banthine was required for a slight reduction of a spasm. Thus on the excised rat ureter, stimulated into spasm by barium chloride, trocinate appears to be, grain for grain, four times as effective as trasentine, octin, and pro-banthine, and five or more times as effective as bentyl and banthine.

It is, of course, conceded that the anticholinergic drugs, bentyl, banthine, and pro-banthine, would effectively relax a muscle from acetylcholine spasm in much lower concentrations, but the rat ureter was entirely unresponsive to acetylcholine and histamine, as revealed by the tracing at the lower right.

Figure 4 repeats on the rabbit ureter most of the tracings made on the rat ureter in figure 3. Again the persistence of a barium chloride spasm of the rabbit ureter is shown by the lower left tracing. Again the unresponsiveness of the rabbit ureter tissue to extreme concentrations of acetylcholine and histamine is shown in the lower right tracing, and the same tissue strip subsequently responds actively to barium chloride.

The rabbit ureter is shown in this slide to respond to the antispasmodic and anticholinergic drugs very similarly to the rat ureter. Again trocinate in a 1:100,000 concentration completely relaxed the ureter stimulated by barium chloride. Again, trocinate proved to be, grain for grain, far more effective against barium chloride spasm than the other drugs with which it was compared: three times as effective as trasentine and five or more times as effective as bentyl, prantal, pro-banthine and octin.

In conclusion, we believe that the synthetic antispasmodics have a definite place in the treatment of spastic ureteritis. We also believe that spastic ureteritis is most probably a muscular spasm of the ureter rather than a spasm of neurogenic origin.

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VESICAL SARCOIDOPSEUDOLITHS (FIBRIN STONES)

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The presence of soft, unattached, endogenous bodies within the bladder or kidneys has been previously described under various names: i. e., fibrin stones, albumin stones, bacterial stones, colloid stones and fibroma. We have coined the term "sarcoidopseudolith" since it rather accurately describes the four flesh colored, soft, spongy, noncrystalline laminated masses found in the bladder of our patient and is descriptive of others appearing in the literature. By definition "sarcoid" refers to an object that is "flesh-like" and since these bodies were free in the bladder, similar to stones, the term "oma" is inapplicable. A stone is defined as a "hard crystalline mass"; therefore, it is necessary that we refer to our noncrystalline vesical bodies as pseudostones or "pseudoliths." Hence, the derivation of the term "sarcoidopseudoliths" or flesh-like false stones.

This extremely rare condition was first described by Marcet in 1818. At the present time the literature reveals 37 cases and of this group sixteen were limited to the bladder. Herein we report the seventeenth case confined to the bladder.

The following table lists the authors and their cases limited to the bladder:

		cases
Elliott, J. W.	1904	1
Ikoma, T.	1924	2
von Lichtenberg, A.	1925	1
Sieoner, E.	1925	1
Blatt, P.	1925	1
Hyman, A.	1928	3
Moore, N. S.	1932	1
Lubash, S.	1938	1
Marcus, R. and Brewer, A. C.	1951	2
Schulte, T. L., Hammer, H. J. and Reynolds, L. R.	1954	3
		16

Joly (1929) and Macalpine (1949) each reported a case of soft calculi in the bladder, but in their description there would seem to have been sufficient crystalline material deposited on the surface of these bodies to question their inclusion in this group.

The cause of this condition is not known, but it is apparent that persistent urinary infection was present in all instances and those limited to the bladder are associated with either recent or immediate vesical obstruction. The most common infecting organisms were staphylococci, streptococci, B. pyocyaneous and the coliform group. Ikoma produced similar masses *in vitro* by using blood and the specific bacteria recovered from one of his patients. The 3 cases reported by Schulte et al. were associated with persistent, low grade, postoperative bleeding with infection following endoscopic resection.

Read at annual meeting, American Association of Genito-Urinary Surgeons, Shawnee-on-Delaware, Pa. May 26–28, 1954.

CASE REPORT

A 62 year old seemingly healthy retired merchant was referred to us by Dr. Louis Mitzlaff for treatment of a severe urethral stricture and an asymptomatic urinary tract infection. The patient was followed for 2 years and his urethral caliber easily maintained at 26F. Irrespective of an adequate urethral caliber the patient continued to have intermittently severe urinary difficulty, but steadfastly refused a urologic survey until urinary urgency and frequency became intolerable.

The patient's past history revealed an episode of urinary retention some twelve years previously due to a urethral stricture. The patient experienced no further disturbance until his present illness.

Upon hospitalization the positive physical findings were limited to suprapubic tenderness and an essentially normal prostate. There was no residual urine and the most significant laboratory finding was severe pyuria which was found to be due to E. coli.

Cystoscopy revealed several large masses in the bladder which were flesh colored and friable. These masses seemed to remain above the cystoscope and were thought to be portions of a huge solid tumor of the anterior bladder wall. The vesical mucosa was peculiarly edematous with a velvety appearance and without ulceration or localized trauma.

Excretory urography demonstrated upper urinary tract dilatation (fig. 1) and an irregular and indefinite filling defect in the bladder. It was concluded that the patient had a large lobulated or multiple tumor of the bladder. Resection of the bladder to remove the tumor bearing area was advised.

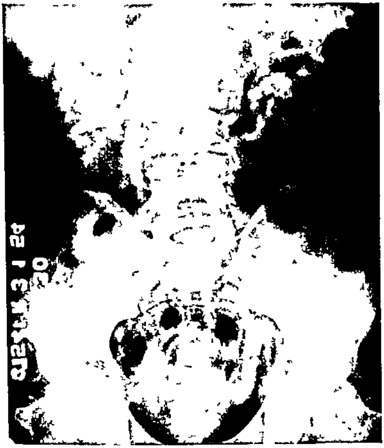

FIG. 1. Excretory urogram demonstrating upper urinary tract dilatation and multiple filling defects in bladder.

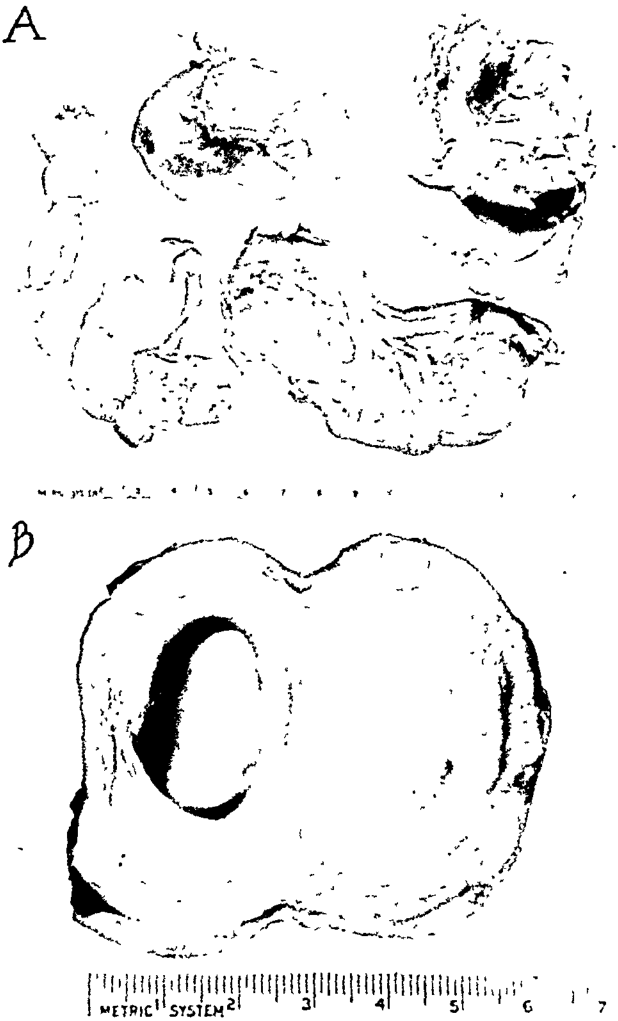

FIG. 2. Group of sarcoidopseudoliths removed at cystotomy

At operation there was no evidence of bladder tumor and there were four soft, flesh-like masses free within the bladder which filled this organ rather completely (fig. 2, *A*). These masses were grayish and pinkish-white, laminated, rubbery bodies resembling an onion and the larger masses were approximately 75 mm. in diameter. The several masses possessed the combined weight of 154 gm. One of the larger masses contained within it a smaller mass floating in a clear fluid (fig. 2, B). The bladder mucosa appeared surprisingly normal with only minimal edema in spite of the persistent urinary tract infection of which we were aware for at least two years. The ureteral orifices seemed elevated and thickened, but the vesical outlet was normal. In concluding the operative procedure the bladder was closed primarily and drained with a urethral catheter.

Histologically the masses removed from the bladder were similar and there were no recognizable epithelial elements. There appeared interlacing mycelial elements and colonies of bacteria, yeast and fungi. The picture resembled that of an inflammatory process involving the growth of organisms in a mat of fibrin and urinary sediment Cultural studies revealed no pathogenic organisms The organisms recovered were large gram-negative and positive rods and a form of Monilia (not albicans)

The patient's postoperative course for 5 days was uneventful, but on the sixth day dyspnea developed and he died suddenly The cause of death was thought to be a massive pulmonary embolus although a necropsy was refused

SUMMARY

The seventeenth instance of bladder sarcoidopseudolith ("fibrin stone") is reported This condition developed in conjunction with a persistent urinary tract infection initiated by a urethral stricture

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VALUE OF PREOPERATIVE RADIATION IN REDUCTION IN SIZE OF SINGLE AND MULTIPLE PAPILLARY BLADDER TUMORS

DANIEL R. HIGBEE

Radiation therapy has lost favor among urologists, especially in the treatment of bladder tumors. This is not because radiation treatment is without benefit, because bladder tumors as a group are fairly radio-sensitive. It is because radiologists have used dosages designed to be maximum in their effect in attempting to cure bladder malignancy, and have ignored the response of the bladder as a functioning organ to the effects of such large roentgen doses. The resultant bladder reactions have been intense, often lasting permanently and disabling the patient more than the original disease. Thus, most of us have been content to employ this form of therapy, if at all, as a palliative measure in the hopeless cases of bladder carcinoma, or as a precautionary or an adjunctive measure against recurrence of malignancy treated by accompanying fulguration or open surgery.

Another limited use of radiation therapy, which I believe is not commonly utilized by us, and which can be employed advantageously in selected cases, is the reduction in the size of single or multiple papillary bladder tumors preparatory to transurethral definitive treatment.

It is commonly agreed that transurethral fulguration, or excision, is the treatment of choice in approximately 65 per cent of accessible and predominantly papillary tumors; and that statistics show the rate of cure for tumors so treated to be exceptionally high. We, therefore, use this method of treatment whenever possible and reserve for open surgery and more radical procedures the more extensive malignancies; either because we fear, due to location, a ureter may be permanently injured, the tumors may be too numerous to cope with transurethrally, they may have penetrated the bladder wall too deeply to be cured by this method, or by their nature and appearance are known to respond better to open or total surgical removal.

A moderately large papillary tumor overlying a ureteral orifice, and with the orifice and tumor base obscured, in spite of bladder distention, catheter manipulation or dye injection, and with a normal excretory urogram, can be reduced in size by the judicious use of x-ray radiation, to one half or one third its former size. Then it can be removed with the orifice and tumor base under vision and without permanent injury to the ureter, even though the tumor base may involve a portion of the orifice.

Multiple papillary tumors which defy diagnosis by cystoscopy and cystogram so far as their number and location are concerned, similarly can be reduced in size sufficiently to treat each individually and adequately even though there may be seven or eight of them in number.

Two methods of accomplishing this are available to us: x-ray therapy with

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high voltage equipment; and radium emanation, usually placed in a Foley catheter.

The dose to be employed should be the maximum mild irritative dose to the bladder as a whole. This usually consists of a tumor dose of about 2500r units of therapy given through multiple portals over a period of approximately 2 weeks, followed by four to six weeks during which regression takes place and during which cystitis, should it develop, may be kept under control by antibiotics.

Radium treatment, if employed with a maximum tumor dose of 3800 mc hours, may be followed by permanent bladder contracture and irritability even if given in three divided doses 6 weeks apart, particularly in elderly people. A dose of 1200 to 2000 mc hours, however, will accomplish the desired reduction in size preparatory to transurethral treatment without these lasting effects, and is particularly applicable to the elderly or debilitated patient, and to those patients who for other reasons would not tolerate x-ray treatment very well.

Cystoscopy then will leave little doubt as to the size of each tumor, its location and proximity to essential bladder structures.

By this method more radical procedures often may be avoided and individuals not suited to more radical surgery still may have adequate treatment. Illustrative cases are depicted in figures 1, 2, 3.

If at the time of re-examination the foregoing outline of treatment does not appear to have been effective other substitute procedures may be employed, or total excision undertaken with better knowledge of the problem involved and with no unfavorable effects from the therapy already utilized.

Certain criticisms may be offered to this method of treatment:

1) Hemorrhage and infection. Hematuria often is present sometime during the course of the therapy. It is occasionally associated with mild cystitis and can be controlled by dispensing with x-ray treatment temporarily and by the use of antibiotics. In 30 cases treated over a period of several years no instances

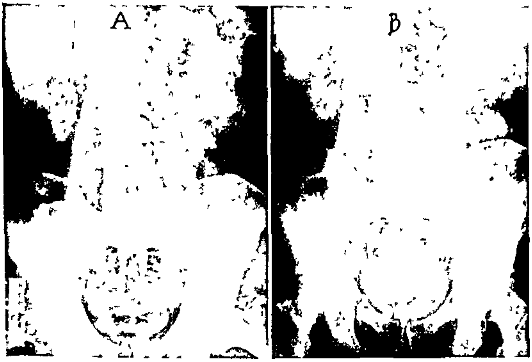

FIG. 1. Excretory urogram; grade 1 tumor. *A*, before x-ray treatment *B*, after x-ray treatment, followed by transurethral resection. Man aged 65. Ureteral catheter used as temporary ureteral splint.

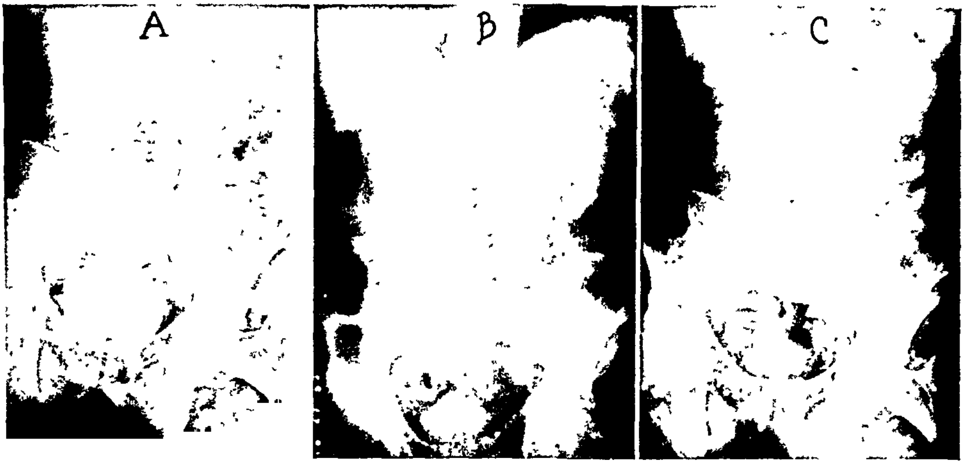

FIG. 2. Excretory urogram; grade 1 tumor. *A*, before x-ray treatment. *B*, during x-ray treatment. *C*, after final fulguration. Man aged 81. Ureteral splint, left ureter, 5 days.

of severe bleeding have required abandonment of the therapy before its completion.

2) During fulguration a ureter may have been injured. The previous radiation greatly reduces the likelihood of such a complication. Should this occur a No. 5 Coudé catheter usually can be passed through the fulgurated area to the kidney and left as a splint for 5 or 7 days, and this should be done as a precautionary measure whenever fulguration encroaches upon a portion of the orifice. In rare instances it may be advisable to fulgurate thoroughly and disregard the effect on the kidney.

3) Some may feel valuable time is lost if other surgery is to be instituted. However, we know that as a rule these tumors neither metastasize nor penetrate deeply into the bladder wall until late. Radiation does tend to block the lymphatics and reduce local growth. If re-examination shows lack of response to treatment, more radical surgery is indicated, or transurethral resection to be followed by radiation therapy if the patient is not suited to other surgery.

4) X-ray treatment may complicate open surgery if such treatment becomes necessary. In these cases the dosage employed is not sufficient to interfere with either the surgery when employed or subsequent healing, as the mild bladder reaction has passed and the dosage has been minimal.

5) Delay in instituting surgery may have caused difficulty in the handling of the patient. This is largely a matter of patient confidence and should not be a problem if one conscientiously strives to maintain the patient's best interests.

6) There is the risk of transplanting tumor tissue to the prostatic urethra. In over 200 cases in which transurethral fulguration has been employed, this complication has occurred but twice in my own experience and then only after repeated bladder fulgurations. Should such a development occur, surgical removal of the prostate is indicated, since in my opinion transurethral excision and fulguration are not permanently effective in prostatic tissue.

7) Recurrences may develop. These can be dealt with by subsequent fulguration if the patient is properly observed in his follow-up treatment.

In spite of these possible drawbacks the method under consideration offers an

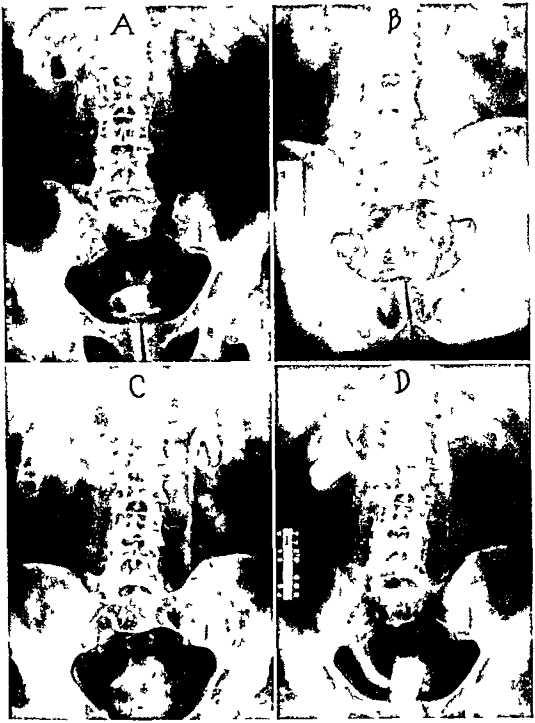

Fig 3 Excretory urogram, grade 1 multiple bladder tumors *A*, suitable for transurethral resection at first examination *B*, 4 months later, tumor suitable for preoperative x ray, followed by transurethral resection *C*, 6 months after initial examination, tumors too far advanced for conservative treatment *D*, present status 3 years after segmental resection and transplantation of left ureter into bladder Man aged 78

additional chance of cure in selected cases, and the avoidance of open surgery in many instances It may be difficult to secure the co operation of a competent radiologist who will hold the treatment within the limits desired and who will adhere to the purpose of the therapy Each patient will necessarily require some variation in his treatment To this end co operation of the patient, radiologist and urologist is required

In conclusion, preoperative radiation in selected cases will reduce the size of the tumor sufficiently to make transurethral treatment the method of choice in a larger number of cases, thus at times avoiding the risks of open surgical intervention yet maintaining a high percentage of cures It is a method particularly suited to moderate sized tumors lying close to or involving a ureteral orifice, to multiple tumors, and to patients whose cases are unsuitable for open surgery

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EXPERIENCE WITH IMPLANTATION OF RADON SEEDS FOR BLADDER TUMORS: COMPARISON OF RESULTS WITH OTHER FORMS OF TREATMENT

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Comparison of results of various methods of treatment of bladder tumors is discouraging and often misleading because comparison of the tumors themselves is at best inaccurate. It would seem that Jewett has proved his thesis that the most important single factor in measuring a tumor's lethal potential is the degree of its infiltration of the wall of the bladder. Probably next in importance comes histologic grading of malignancy (Broders). Other important factors include presence or absence of metastasis, including metastasis to the prostate (Reynolds, Schulte and Hammer), size and location of the tumor and involvement of the ureteral orifices or vesical neck. If such information is obtained at open operation (when total or partial cystectomy is performed, so that the bladder wall is available for gross and microscopic examination) it may be considered reasonably accurate. Data so derived may furnish a "base line," standard of "measurement" or "classification" of sufficient accuracy to permit comparison of groups of cases.

Such is not the case, however, when open exploration is not carried out. Here one must rely on "indirect" or "clinical" data, such as transurethral biopsy, bimanual examination to determine degree of infiltration and cystoscopic examination to determine size and location of the tumor. We have not been as greatly impressed as Jewett has been with the accuracy of bimanual examination. For instance, one may be certain that an indurated, fixed mass in the region of the base of the bladder, felt on bimanual examination, indicates perforation of the bladder wall by the carcinoma. However, less prominent degrees of abnormality on palpation in a given case may be described, or interpreted, in different ways by as many examiners. Metastasis (unless of advanced degree) cannot be easily detected. Evidence of ureteral obstruction obtained by excretory urography usually suggests serious infiltration of the bladder wall. All of the above data, though helpful, are too inaccurate to permit precise comparison of tumors.

The results of treatment with total and partial cystectomy have been so discouraging, however, that the present trend of treatment appears to be away from open surgery and towards transurethral methods. Because of this we are going to be forced to rely more and more on "indirect" or "clinical" data so that comparisons of tumors and their treatment must be accepted with reservation. This, no doubt, is one of the most important reasons for the wide variation in results of similar types of treatment reported from various clinical centers. It

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is this inability accurately to measure, classify or establish a "base line" that has deterred us from attempting statistical appraisal of the results of treatment in our large Mayo Clinic group of well-followed cases of bladder tumor The few reports from the clinic of small, selected groups of cases which have been made in recent years (Ferris and Priestley, 1948, McDonald and Thompson, 1948) have been concerned only with tumors which have been exposed by open exploration for the purpose of total or partial cystectomy

Before proceeding with our study of the limited group of patients we have treated at the clinic with radon implantation, a brief summary of current articles dealing with results of modern treatment of bladder tumors should form an interesting, although admittedly inaccurate, basis for comparison The summary for the most part is limited to groups of cases which have been analyzed on a standard statistical basis (5-year survival) It should be noted that in all of the series of cases referred to in this summary, "benign papillomas" (papillary tumors, grade 1, Broders) have not been included

REPORTED EXPERIENCE

Radium, radon Barringer's extensive experience (1937–1947) with implanted radon seeds supplies the best figures available for this type of treatment He expressed preference for segmental resection for tumors of the upper half, vault, of the bladder, and implanted radon for those of the lower half Cystoscopic implantation, repeated at intervals, if necessary, is employed for small, easily accessible tumors, and suprapubic implantation for larger ones Barringer and Dean standardized the dose of 2 millicurie seeds implanted 1 cm apart, or closer if of less strength They warned against insufficient dose, which is the commonest cause of failure, and Barringer wrote, "Seeds even 0 25 cm apart can do no harm " Barringer's most recent appraisal (1952), of 221 traced patients treated more than 5 years before, showed that 35 7 per cent of them had survived 5 years or more or had been "cured " Broken down into types of tumor, of 94 patients who had papillary carcinoma, 49 (52 per cent) lived 5 years or more, whereas only 30 (23 6 per cent) of 127 patients who had infiltrating carcinoma survived so long Marshall (1947–1950) recently has questioned the accuracy of these figures[1] but they seem to be generally in accord with similar well studied groups from other clinics

J L E Millen (England, 1949–1950) expressed the belief that radon seeds are the treatment of choice for bladder tumors He reported 45 per cent 5 year survivals among 117 patients with bladder tumor, 69 of which were noninfiltrating and 48, infiltrating Of patients with noninfiltrating tumors, 63 per cent survived 5 years or more, as compared with 21 per cent of those with infiltrating tumors Milner (1953), who in recent years has made an admirable effort to evaluate various types of treatment of bladder tumor, reported that 18 4 per cent[2] of patients who underwent combined transurethral removal of bladder tumors and implantation of radon survived 5 years or more. Barnes, Turner and Bergman (1946), although they offered no statistics that could be used on a 5-year follow-up basis, demonstrated that, in their hands, transurethral removal and radon gave better results and longer survivals than did transurethral removal only. Dean and Balfour (1940), studying the results of both radon and roentgen therapy in 100 cases of bladder tumor (50 papillary and 50 infiltrating), found that 54 per cent of patients who had papillary tumors, and 14 per cent of those who had infiltrating tumors, survived 5 years or more. They did not separate the patients into those treated by roentgen rays and those treated by radon.

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[1] Marshall estimated that only 17 3 per cent of this group of patients survived 5 years or more Moreover, he stated that most of these patients "merely survived " He estimated that only 9 2 per cent were controlled sufficiently to enable them to be considered as examples of successful 5 year results "

[2] This figure would be somewhat higher if it were based on percentage of traced patients (as are most reports) rather than on the total number of patients

Moore (1947) reported that 69 (44 per cent) of his series of 157 patients with carcinoma of the bladder were treated with radium or radon or both. Only 31 of the 69 patients were followed for 5 years; 13 were living (41 per cent of traced patients). He mentioned a patient with a huge, infiltrating, apparently inoperable carcinoma of the bladder, who was treated with radon seeds for palliation only but who was cured and alive 18 years following treatment.

Radium element (needles) has been held less in favor in recent years than radon seeds. Jacobs (Glasgow, 1949) expressed the belief that radium needles are superior to segmental resection for tumors of the lower half of the bladder. Of 110 patients so treated, he found that 37 (34 per cent) lived 5 years or more. He stated that this method of treatment is superior to segmental resection (partial cystectomy) which, he stated, yielded only 20 per cent 5-year survivals. Lenz, Cahill, Melicow and Donlan (1947) reported that 20 per cent of 46 patients treated with radium needles survived 5 years or more. Kligerman, Robinson, Fish and David (1952) compared the results of segmental resection and use of radium needles in a group of 347 patients (149 segmental resection and 198 radium) in which treatment was given prior to 1950. Of the combined group of 347 patients, 37 per cent lived 5 years or more. To make the comparison of the two forms of treatment they then eliminated 137 cases in which the lesions were "inoperable" and in which they considered treatment to be palliative only. In the remaining 210 "definitive" cases (91 radium and 46 segmental resection) their figures for 5-year survival with "clinical arrest" were 38.1 per cent for radium and 22.3 per cent for segmental resection. For infiltrating tumors, therefore, they preferred radium to segmental resection. O'Conor (1950) made the statement, "The implantation of radium, either as needles or as radon seeds, was abandoned in this clinic 14 years ago. A thorough trial in many patients convinced us of the inadequacy of this method." No supporting statistics are included in the article.

Roentgen rays. Roentgen therapy continues to be regarded chiefly as a palliative procedure in more or less "hopeless" cases, or as an adjunct to other forms of treatment. Colby and Sniffen (1946) reported on a series of 130 patients treated with roentgen rays (1,200 kilovolt unit). "Only those tumors which were not suitable for local destruction, excision or radium implantation were treated." A total dose of 6,000 r was employed. The tumors in these cases were almost equally divided between papillary and nonpapillary types. Only 7 patients (5 per cent) survived 5 years or more.

Partial cystectomy (segmental resection) and total cystectomy. Riches (England, 1949) mentioned that 21.7 per cent of patients who underwent segmental resection lived 5 years or more. Jacobs also mentioned this percentage. Milner (1953) reported that approximately 24[3] per cent of patients who underwent segmental resection lived 5 years or more but only 1 of 16 who underwent total cystectomy survived so long.

To Jewett (1947–1953) must be given credit for calling attention to the importance of the degree of infiltration of the tumor as regards prognosis and response to treatment. He pointed out that superficial infiltration of the bladder wall (less than half way through the muscle) carries an infinitely better prognosis than deep infiltration (involvement of the entire bladder wall). In a recent (1953) comparison of partial and total cystectomy for infiltrating tumors based on degree of infiltration by the tumor his results were the following: Among 95 patients with infiltrating carcinoma of the bladder treated by either partial or total cystectomy there were 20 (21 per cent) 5-year survivals. However, if these patients are divided into two groups depending on whether infiltration was superficial or deep, results were as follows: Of 22 patients whose tumors infiltrated superficially, 15 (68 per cent) lived 5 years or more, as compared to only 5 of 73 patients (7 per cent) whose tumors were deeply infiltrating. Parenthetically, the overwhelming proportion of deeply infiltrating tumors in this series should be noted. This should be taken into consideration when evaluating percentage reports of 5-year survivals among series of patients treated by transurethral resection. Such series usually contain a much higher percentage of cases in which infiltration was superficial or the tumors were papillary and there was no infiltration. As far as partial versus total cystectomy is concerned, of the 95 patients with whom Jewett was concerned, 49 were subjected to total cystectomy and 18.3 per cent lived 5 years or more; 46 underwent partial cystectomy and 23.9 per cent of them lived 5 years or more.

Further evidence of the importance of degree of infiltration was supplied by McDonald and Thompson (1948) who studied a group of 274 patients with bladder tumor at the Mayo Clinic. Each patient had been subjected to either partial or total cystectomy, so that the bladder or a portion of it was available for gross and microscopic study. All except 31 showed evidence of infiltration of the bladder wall. Two hundred forty-three patients traced 5 years formed the basis of the report. For the entire group the 5-year survival rate was 29 per cent. Broken down as to type and presence or absence of infiltration, following are the figures for 5-year survival: 69.5 per cent of patients who had papillary tumors without infiltration; 34.5 per cent of those who had papillary tumors with infiltration; 18.7 per cent of those who had nonpapillary tumors, all with infiltration. Further study of infiltrating tumors from the standpoint of depth of infiltration showed this interesting distribution of 5-year survival: 38.3 per cent of patients who exemplified submucosal infiltration; 29.6 per cent of those who exemplified infiltration into muscles; 5.2 per cent of those who exemplified perforation of the bladder and involvement of perivesical fat.

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[3] This figure would be somewhat higher if it were based on percentage of traced patients (as are most reports) rather than on the total number of patients.

Kerr and Colby (1951) studied a series of 135 patients treated either by partial or total cystectomy. Of the 107 patients whose tumors infiltrated the muscular coat of the bladder, only 10 per cent survived 5 years or more, whereas 64 per cent of the 28 whose tumors did not infiltrate survived 5 years or more. Of the entire series of 135 patients, 29 (21.4 per cent) survived 5 years or more. In this study, partial cystectomy seemed to be more effective than total cystectomy. Especially was this apparent relative to noninfiltrating tumors. Whereas 100 per cent of 16 patients with no infiltration survived 5 years or more as a result of partial cystectomy, only 2 of 12 such patients (16 per cent) survived so long following total cystectomy. *The other 10 died from uremia secondary to ureteral obstruction resulting from the uretero-intestinal anastomosis.* Jewett (1947–1953) also reported that all of his 9 patients who survived 5 years or more after total cystectomy gave evidence of varying degrees of renal damage. Kerr and Colby (1951) also concluded that infiltration was more important than histologic grade of malignancy or size of tumor, as far as survival was concerned.

The ineffectiveness of total cystectomy as a means of curing carcinoma of the bladder is further demonstrated in the report, by Ferris and Preistley (1948), of a series of 119 cases of bladder tumor in which total cystectomy was performed at the Mayo Clinic. Only 19 per cent of the traced patients survived 5 years or more. Marshall's figures (1947–1950) (although not based on 5-year survival) are equally discouraging. One reason for the failure of total cystectomy is that, in roughly 40 per cent of cases in which the musculature of the bladder is deeply infiltrated, metastasis has taken place and eventually causes death. Patients whose tumors have not deeply infiltrated and metastasized eventually die from damage to the upper part of the urinary tract secondary to the uretero-intestinal anastomosis; this was mentioned previously. Jewett found that of 89 tumors which had deeply infiltrated the muscle, 52 (58 per cent) had metastasized, whereas only 1 of 18 of which the infiltration was superficial or submucosal had metastasized. As an adjunct to total cystectomy, Leadbetter and Cooper (1950) have advocated extensive block dissection of the pelvic lymphatic structures and removal of lymph nodes that lie along the common iliac blood vessels. Marshall also is exploring the possibility of this avenue of approach.

Transurethral operation. As has been explained, results of transurethral resection and fulguration cannot be as accurately analyzed as those of partial or total cystectomy. Milner (1953) found that 20.6[4] per cent of 141 patients, treated by transurethral resection or fulguration only, lived 5 years or more. He used his special technique to obtain, with the loop resectoscope, a piece of tissue adequate for microscopic study and he estimated that the tumors of 57 of the patients could be classified as having deeply infiltrated the muscularis.

Flocks (1946–1951) and his group have had experience with a large number of patients subjected to transurethral resection. Unfortunately, their reports are not made on the standard 5-year survival method; so it is almost impossible to compare the results with those of other studies. However, in Flocks' (1952) discussion of Jewett's paper is this statement: "In a group of 50 consecutive cases which would fall into group B-1 (superficial infiltration of muscularis) as he [Jewett] classified them, there were 56 per cent five year survivals. On the other hand, those that fell into group B-2 (deep infiltration of the muscularis) showed a very negligible percentage of five year survivals, approximately 3 per cent, so that this would fit in with his results." In a series of 540 patients (those with papillomas grade 1 excluded) Flocks evaluated survival of patients who received "all types" of treatment, on the basis of *"four year controls,"* as follows: patients who had papillary carcinomas, 77.4 per cent; infiltrating carcinomas, 39.7 per cent; infiltrating and perforating carcinomas, 1.6 per cent (combined 4-year survival rate, 42.8 per cent). Again, he mentioned that 367 of the 540 patients were treated by transurethral resection alone, with a 66 per cent "control" of traced patients. In spite of the fact that these analyses are not made in a form comparable to 5-year survival studies, still Flocks' results appear to be superior to any so far published. A re-evaluation of his cases, with use of a standard statistical method, would be a distinct contribution to the subject.

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[4] This figure would be somewhat higher if it were based on percentage of traced patients (as are most reports) rather than on the total number of patients.

Summary of statistics from the literature. If this incomplete summary is at all representative, the majority of workers are reporting 5-year survival rates which vary from 20 to 35 per cent of traced patients. This includes all types of treatment of all types of carcinoma of the bladder except papillomas grade 1. Flocks' results, with special emphasis on transurethral resection, appear to be better than this. Apparently the studies mentioned substantiate the statement of Ash, (1940) that roughly a third of patients with carcinoma of the bladder can look forward to a 5-year survival.[5] Weight of opinion now favors degree of infiltration of the tumor as the most important single factor in survival, although size of the tumor, its location, its grade of malignancy, the presence or absence of ureteral obstruction and the presence or absence of metastasis, all are important. With this background, we present below our experience with implanted radon seeds in a selected group of cases.

EXPERIENCE WITH IMPLANTATION OF RADON SEEDS IN 118 CASES OF BLADDER TUMOR

That radium and radon therapy never has been a favored method of treatment for bladder tumors at the Mayo Clinic is illustrated by Thompson's (1952) figures on 1,222 consecutive cases seen in the period 1946–1950 inclusive. The methods of treatment and the number of cases in which they were used were as follows: total cystectomy, 117; segmental resection, 60; suprapubic excision or fulguration or both, 23; implantation of radon seeds, 61, and transurethral procedures, 961. Radium element (needles) was not used. The 61 cases in which radon seeds were implanted represent only 5 per cent of the series.

In all fairness to the procedure it should be said that we in the Section of Urology at the clinic have never been enthusiasts in the use of radon seeds. We have reserved this form of treatment as palliation for inoperable tumors, or for use in cases in which the risk of open operation was excessive, and the size and location of the tumor interfered with complete transurethral removal. In most cases the radon has been implanted cystoscopically, and although in some cases it has been implanted again at a later date, we have not been as diligent in using radon treatment to the limit of its effectiveness as have workers such as Barringer, Dean, J. L. E. Millen and others. Nevertheless, on several occasions we have been confronted with a patient in excellent health who had been sent home, we thought to die, several years previously, after we had implanted radon seeds as a purely palliative procedure. Hence, this study was undertaken.

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[5] It is of interest that Welch and Nathanson stated that the 5-year survival rate of patients with untreated carcinoma of the bladder is approximately 10 per cent

Material. We have studied records of all Mayo Clinic cases of bladder tumor in which radon seeds were implanted, either cystoscopically or suprapubically, from January 1, 1935 to December 31, 1948 inclusive. All except 3 patients were traced for 5 or more years. There were 118 patients in the series, of whom 105 were males and 13 females. In 89 (75 per cent) of the cases the radon was implanted cystoscopically and in 29, suprapubically. Ninety-nine of the patients were in the age group 40 to 70 years inclusive; the largest number (41 patients) were between 60 and 70 years of age, inclusive.

Gross characteristics. Inasmuch as three fourths of the patients were *not* subjected to suprapubic exploration, in the majority of cases the lesions had to be appraised chiefly by "indirect" or "clinical" data. On the basis of size, we defined three groups: small (2 cm. or less in diameter), 11 cases; medium (2 to 4 cm. in diameter), 50 cases; large (more than 4 cm. in diameter), 57 cases. In general, then, the tumors were extensive. As far as cystoscopic appearance of the tumor was concerned, 102 appeared to be either "sessile" or "solid," whereas 16 appeared papillary. More than one region was involved in some cases. The trigone and base were involved in 68 cases; the lateral walls in 67; the posterior wall in 16; the dome in 5 and the vesical neck in 21.

Histopathologic data. Material for biopsy, obtained transurethrally or at open operation, was re-examined for this study by Dr. J. R. McDonald and his associates in the Section of Surgical Pathology. The data are recorded in the table. The footnote to this table should not be overlooked in view of the fact that McDonald and Thompson (1948), in their study of material obtained by partial and total cystectomy, found that practically all nonpapillary tumors infiltrated the bladder wall.[6] Therefore, it may be assumed that practically all of the 106 tumors in groups B, C and D (table 1) were infiltrating to some degree. From these data, however, we are unable to say how many tumors could be classified as examples of superficial infiltration of the muscle and how many as deep infiltration.

That considerably less than a third of the tumors were papillary demonstrates that principally the more seriously infiltrating types of tumors were subjected to implantation of radon. Of interest is the preponderance of lesions grades 3 and 4 in the infiltrating groups (B, C and D) as compared with the grade 2 tumors (only 22 out of 106).

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[6] They also demonstrated that all adenocarcinomas, pure or mixed, infiltrated the wall and that the same was true concerning 93 of 94 squamous cell carcinomas.

TABLE 1 *Histopathologic characteristics of 118 bladder tumors treated by implantation of radon seeds*

Classification as to (1) Papillary or Nonpapillary (2) Infiltrating or Noninfiltrating*		Transitional Cell Epithelioma (Total Cases 92)	Squamous Cell Epithelioma (Total Cases 23)	Adenocarcinoma (Total Cases 3)
Group A, papillary (12 cases)	Grade of malignancy, (Broders)			
	1	3		
	2	5		
	3	3		
	4	1		
		Subtotal 12		
Group B, papillary with infiltration (15 cases)	1	0		
	2	5		
	3	9		
	4	1		
		Subtotal 15		
Group C, nonpapillary (28 cases)	1	0	0	0
	2	5	3	0
	3	6	5	2
	4	7	0	0
		Subtotal 18	8	2
Group D, nonpapillary with infiltration (63 cases)	1	0	0	0
	2	5	4	0
	3	22	7	1
	4	20	4	0
		Subtotal 47	15	1

* Very likely, many of the tumors in group C were infiltrating, but the instrument used in taking the specimen for biopsy did not cut deep enough to include a portion of the bladder wall and demonstrate the infiltration Of the specimens for biopsy 75 per cent were obtained cystoscopically

Operability We classed as "inoperable" any condition in which one or more of the following could be demonstrated 1) definite induration and fixation of the base of the bladder, on bimanual examination, 2) obstructed ureter or ureters, 3) direct evidence of perforation of the bladder wall by the tumor, on suprapubic exploration, and 4) death within 6 months after treatment On this basis, in 54 of the 118 cases the condition could be considered inoperable Of the 54 inoperable lesions, microscopic diagnosis of material obtained at biopsy disclosed that 40 of the tumors were infiltrating, of these, the malignancy of 35 was of grade 3 or 4 and of only 5 was it of grade 2 "Noninfiltrating"[7] tumors numbered 14, of these the malignancy of 10 was of grade 3 or 4 and of only 4 was it of grade 2 In 33 of these 54 cases ureteral obstruction was demonstrated but, in 15 of the 33, other factors of inoperability also were present. In our opinion, ureteral obstruction usually signifies serious infiltration of the wall of the bladder.

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[7] It should be emphasized that "noninfiltration" in a specimen for biopsy removed transurethrally means nothing because a suitable area of the bladder wall may not be represented in the portion obtained for examination

Treatment. Of the 118 patients, 43 had had some form of treatment, either at the clinic or elsewhere, before the radon seeds were implanted. In most cases this consisted of ineffectual cystoscopic fulguration. The radon seeds were implanted cystoscopically in 89 cases and suprapubically in 29. Gold seeds were used. In the majority of cases the number of seeds varied from 6 to 20. Most of the seeds we used varied in strength between 1 and 1.6 millicuries. The amount of radon employed in most cases was 11 to 20 millicuries. Probably we erred on the side of insufficient radiation in many cases. Although we tried to implant seeds at the prescribed spacing of 1 cm., we feel sure that in many cases they were implanted much closer, in fact as close as 0.25 cm. apart in some cases. It is, of course, impossible, cystoscopically, to place every seed accurately. Most of the time it is impossible to see where a seed has been implanted;, therefore the operator must make a mental diagram of implantation and remember where each seed was placed. In large lesions this is difficult. An attempt was made to implant the seeds at a depth of about 0.75 to 1 cm. In only 16 cases was subsequent implantation of radon seeds carried out; once only in 14 cases and more than once in 2 cases.

Associated treatment: In many of these cases some other form of treatment also was used in conjunction with implantation of radon, as follows: transurethral resection of the tumor with the loop resectoscope, 16 cases, and with the Thompson resectoscope, 20 cases; transurethral fulguration, 30 cases; suprapubic fulguration or excision of the tumor, with a cutting loop, 16 cases. This makes a total of 82 cases in which part of the tumor was destroyed or removed by other means than radon. In nearly all cases resection of the tumor was considered incomplete or radon seeds would not have been implanted.

Associated roentgen therapy: In 64 of the 118 cases roentgen therapy was used in addition to implantation of radon. In 30 of these cases the roentgen therapy was given at the same time as the radon was implanted or within 3 months before or after the implantation. In 25 cases it was given subsequently only, while in 9 cases it was administered both concurrently and subsequently. Dr. Martin Van Herik, of the Section of Therapeutic Radiology, has calculated the total tumor dosage of roentgen rays received by these patients and has placed them in three groups: low (1,200–1,750 r), 28 cases; medium (2,200–3,300 r), 20 cases, and high (4,000–6,000 r), 16 cases. Those patients who received a "low" dosage of roentgen rays could be considered as having been treated for palliation only, so far as roentgen therapy is concerned. Any curative results in this group of patients are probably due largely to the effects of radiation delivered by implanted seeds. We used the roentgen therapy because we often thought that our inability accurately to determine the thickness of the tumor by cystoscopic means, resulted in not placing some of the seeds sufficiently deep to destroy all of the tumor.

Cystoscopic appearance of bladder following implantation of radon seeds: In nearly all cases in which radon seeds are used, a local area of necrosis results, which often is covered with lime salts, encrusted material, or even calculi. At each 3-month examination, we scrape away this necrotic material with the heel of the Braasch cystoscope and then, with the sharp specimen forceps, we remove pieces of tissue from the base and periphery of the lesion. Nearly always, surrounding this necrotic area, is some erythema and edema which should not be confused with evidence of recurrence, but biopsy is necessary to make sure. Six months to a year or more may pass before this "slough" has entirely separated and the bladder has healed. It is seldom, however, that "recurrences" or residual, uncontrolled tumor, if present, cannot be identified within 6 to 9 months.

Postradiation cystitis: There has been much discussion in the literature, both pro and con, regarding postradiation cystitis. In reviewing the records of these 118 patients we could not find definite evidence of unusually severe, painful vesical irritation which could be attributed solely to the radon seeds. In a few cases, moderate dysuria continued because of uncontrolled tumor. In 2 cases severe postradiation pain was caused by the uncontrolled tumor, which invaded the trigone, perforated the bladder and metastasized to the prostate gland and elsewhere. In a few cases the bladders became of small capacity and micturition was frequent, but in these cases roentgen therapy also had been given. In our experience, contraction of the bladder is a not uncommon sequel of roentgen therapy, especially if curative doses have been administered. In short, we were not impressed with the importance of postradiation cystitis in this series of cases.

Of the 118 patients, all were traced at least 1 year and 115 were traced 5 years or more after treatment. Of these 115 patients, 33 survived 5 years or more. This represents 29 per cent of 5-year survivals, which compares favorably with any type of treatment reported so far in the literature for bladder lesions of this general type. Also, this is approximately the same percentage of 5-year survivals reported by McDonald and Thompson (1948) for the series of 274 Mayo Clinic patients who were subjected to total or partial cystectomy (243 traced).

Twenty-six of the 118 patients never had subsequent cystoscopic examination, apparently, because the tumor was not controlled and the patients failed rapidly; 20 of them were dead within the year. Of the other 6 who were not re-examined, 4 died between 1 and 5 years after treatment. Two survived 5 and 6 years respectively.

Eleven other patients were re-examined cystoscopically within the first year after treatment, and either nothing noteworthy was found or the condition seemed controlled. They never were examined thereafter, however. Four of these patients died within the first year, 5 in the second year and 1 in the third year. One was living and well 14 years although he never had submitted again to re-examination of his bladder.

Eighty-one patients were examined periodically in our routine manner. Thirty-one of these 81 patients died within the first year after operation. If this figure is added to the 20 and 4 mentioned a few lines back, who died in the first year, then 55 (or 46 per cent) of the 118 patients are seen not to have survived the first year after treatment.

Fifty patients (81 minus 31) whose bladders were re-examined periodically survived more than 1 year after treatment. Of these 50, the tumors of only 10 recurred as follows: 5 in the second year after treatment, 2 in the third year and 1 in the fourth year, while the tumors of 2 more did not recur until the tenth and fourteenth years respectively. These latter 2 cases probably represent new tumors rather than recurrences. This leaves 40 patients who were re-examined periodically by cystoscopy and whose bladders, at the most recent report, were negative to examination. Twenty-four of these patients lived more than 5 years after treatment, 13 died before 5 years had elapsed, while 3 were untraced for the entire 5-year period.

From the above data it is apparent that, in most cases, "recurrences" or residual uncontrolled tumors become apparent within the first 2 years after treatment, and the overwhelming majority within the first year. Therefore, patients who are free of tumor for more than 2 years have an excellent chance of remaining free of it, although, of course, they may die of distant metastasis as well as of causes unrelated to the bladder tumor.

CONSIDERATION OF DATA REGARDING THE 33 PATIENTS WHO SURVIVED 5 YEARS OR MORE

General data. It should be of interest to try to ascertain factors which predisposed to the favorable outcome in the 33 cases in which the patients lived 5 years or more after operation. *Size of the tumor* did not appear to be important, for 16 tumors were of medium size, 8 were large and 9 were small. All *locations* in the bladder were represented. In all 33 cases, the condition was considered operable, except in 7 in which it was considered inoperable solely on the basis of ureteral obstruction. From the standpoint of microscopic examination of material obtained for biopsy, 20 of the tumors were definitely infiltrating and were of the following grades of malignancy: 6 tumors, grade 2; 14 tumors, grades 3 and 4. In 13 cases, infiltration could not be demonstrated from the specimen obtained for biopsy. Of these, in 7 cases the tumors were of grade 3; in 2, of grade 2, and in 1, of grade 1. In only 4 of these 13 cases were the tumors papillary; probably all of the other 9 would have given evidence of infiltration if adequate material for biopsy had been available. In 7 cases, implantation of radon seeds was done suprapubically and, in 26, cystoscopically. Radon was implanted subsequently once in each of 5 cases and more than once in 2 others. Roentgen therapy was given to 14 patients, which is approximately half of those who lived 5 years or more. This is roughly the same incidence of roentgen therapy as that which obtained in the entire group. In 9 cases the dose of roentgen rays was low; in 2, medium and in 3, high. In practically all of the 33 cases, by some means such as fulguration or transurethral or suprapubic resection, partial removal, or incomplete destruction, of the tumor was effected a few days before, or at the same time as, the radon seeds were implanted.

Degree of control of patients who survived 5 years or more. It seems important to know whether the 33 patients who survived 5 years or more "merely survived" (a term recently employed by Marshall) or were adequately "controlled," "arrested" or "cured," in this period. To clarify this matter, the cases have been divided into 2 groups: 1) 15 patients who are dead at this writing and 2) 18 patients who are living. Each group will be considered separately.

Of the 15 dead patients, 11 had no recurrence following the radon treatment. This includes 3 patients who underwent a second implantation. Recurrences appeared in the remaining 4 cases as follows: In 1 case, there were yearly recurrences for 5 years; these responded to fulguration. Then no recurrences were noted for 5 years. The patient died of a coronary attack 10 years after the original treatment. In 1 case recurrences appeared in the first 2 years and were treated with fulguration and 1 subsequent implantation of radon. No further recurrences were noted and the patient died of a stroke 5½ years after the original treatment. In 1 case the tumor recurred in the third year and was never thereafter adequately controlled. The patient died 5½ years after the original treatment. In 1 case recurrences developed 1 year after treatment. Further examinations were not made, but apparently the patient was free of symptoms and died from a coronary accident 6 years after the original treatment. At necropsy, no evidence of recurrence was seen in the bladder, but extravesical metastasis was found to have taken place. The causes of death of 11 of the 15 patients could be determined fairly accurately. They were carcinoma of the bladder in 4 cases, cerebrovascular accident in 3, coronary occlusion in 3 and carcinoma of the stomach in 1. The causes of death of 4 patients are unknown.

Of the 18 living patients, 11 never have given evidence of recurrence of the tumor. A summary of the remaining 7 is as follows: The "recurrences" in 3 cases came extremely late after treatment (11, 14 and 14 years respectively), so that the growths probably should be considered "new tumors" rather than recurrences. Data on the remaining 4 cases follow: In 1 case the first recurrence appeared 3 years after treatment. Transurethral fulguration was applied and, at the time of writing, the patient had been 4 years without recurrence (7-year survival). In 2 cases recurrences appeared periodically for several years, but apparently were adequately controlled by transurethral fulguration. These patients have survived 10 and 14 years respectively. In the remaining case, 2 courses of roentgen therapy were given 3 and 4 years after the radium, for a recurrence that was considered questionable at the time and that could not be proved on cystoscopic biopsy. A total tumor dose of 4,375 r was given. Total cystectomy was done 4 years after the biopsy, elsewhere, because of an extremely contracted bladder. We have been unable to find out whether any residual tumor was found.

It appears, therefore, that in addition to surviving at least 5 years, the vesical lesions of these 33 patients have, in general, been satisfactorily "controlled." Also of interest is the length of survival of these 33 patients, as follows:

Of the *15 patients who are dead,* survival after treatment was as follows: 5 years, 6 patients; 6 years, 2 patients; 7 years, 3 patients; 8 years, 1 patient;

9 years, 1 patient and 10 years, 2 patients. Of the 18 patients who are alive, survival was as follows: 5 years, 2 patients; 6 years, 1 patient; 7 years, 3 patients; 9 years, 1 patient; 10 years, 2 patients; 11 years, 1 patient; 14 years, 5 patients and 15, 16 and 17 years, 1 patient each.

CONCLUSIONS

The present status of the treatment of bladder tumors (benign papilloma—papillary tumors grade 1, Broders—excluded) has been appraised by a summary of current literature.

The 5-year survival rates for partial and total cystectomy appear to be approximately 30 per cent. Partial cystectomy appears to give results superior to those of total cystectomy. Degree of infiltration of the wall of the bladder is the most important factor in prognosis, with the microscopic grading of degree of malignancy next in importance.

The results of transurethral and radiation therapy are difficult to compare with those of total and partial cystectomy because tumors cannot be accurately "measured" and "classified" without surgical exploration. Only by this latter procedure can degree of infiltration and presence or absence of metastasis be accurately determined. In spite of this difficulty of establishing a base line for "nonoperated" tumors, the literature suggests that, for the present at least, the results of transurethral removal of tumors are probably superior to those of open operative procedures.

A study was made of 118 cases in which radon seeds were implanted for bladder tumor at the Mayo Clinic. As near as we can determine, the tumors in these cases were of comparable "severity" or "lethal potential" to those treated by total or partial cystectomy in the Mayo Clinic series reported by McDonald and Thompson (1948). The incidence of infiltration was less than in Jewett's series of cases. In three fourths of the cases the radon was implanted cystoscopically. In approximately three fourths some type of partial removal or fulguration of the tumor (either cystoscopically or suprapubically) was carried out in addition to the implantation of radon. In slightly more than half of the cases, some x-ray therapy also was given, although in most cases only a low palliative dose was administered.

We were surprised with the results of this radon treatment. Although 46 per cent of patients did not survive the first year, 29 per cent of 115 who were traced survived 5 years or more, which is approximately the same percentage of 5-year survival reported for total and partial cystectomy by McDonald and Thompson (1948). In the large majority of cases, recurrences or the presence of uncontrolled tumor became apparent within the first 2 years (most within the first year). A patient surviving 2 years without recurrence has an excellent chance to survive 5 years or more. Postradiation cystitis was not a troublesome complication in this group of cases. Patients who survived 5 years or more appeared to be comfortable and well "controlled" as far as bladder function was concerned.

As a result of this study, we are inclined to feel, as do Barnes, Turner and Bergman, that the combined treatment of transurethral removal plus implantation of radon seeds may merit more frequent use than it has been accorded in the past

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TREATMENT OF BLADDER NECK CONTRACTURE BY PLASTIC OPERATION

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Contracture at the bladder outlet often comprises a vexing problem of treatment because the condition tends to recur. There are, of course, many conditions that fall under the general heading of bladder neck contracture and when the cause is spasticity or hyperplasia of the internal vesical sphincter the results of any form of surgery are usually excellent. But when cicatrization is the basis of contraction, there is often deep seated tissue involvement at the entire bladder neck which not only causes a diminution of the urethral caliber but also a shortening of the urethra and often too, the ureters are drawn down into the bladder outlet.

Most urologists have had the experience of treating patients who are beset by this condition. The patient complains of typical obstructive symptoms, or in some instances his complaint is related more to long standing infection. Endoscopic examination reveals the presence of a contracted bladder outlet or just an elevation of the posterior vesical lip in the form of a fibrous bar. In recent years all urologists have agreed that this condition is best treated by endoscopic resection. However, many experienced resectionists have held the view that the most of their bad results have occurred in this group of patients. The recurrence rate is high and endoscopic examination of the recurrent case reveals a new contraction ring or bar of tissue and in extreme cases there may be only a filiform size orifice at the bladder outlet. The constrictive tendency of the tissues is so great that further treatment by enlarging the channel from within is followed by prompt contraction and recurrent obstruction.

A suprapubic operation long used for treating contracture consisted of removing a wedge of tissue from the posterior vesical lip but this procedure fared little better than Young's punch operation. Many surgeons have resorted to total or radical prostatectomy either by the perineal or the retropubic approach. In some instances this method has resulted in cure but radical surgery has often been contra-indicated because the abnormal position of the ureters has made them vulnerable to injury, or because the patient has been reluctant to face sexual impotence.

Dr. Bradford Young of San Francisco described a new technique for the treatment of bladder neck obstructions in children which appeared to be particularly applicable to the problem under our present consideration. His operation applies the Heineke-Mikulicz principle for enlarging the bladder outlet (fig. 1). He uses a short midline incision in the bladder just above its junction with the urethra, then extends the incision down into the prostatic urethra in male patients, and in the female it is extended for a short distance into the urethra. Through this opening the surgeon is able to look for valves in the urethra

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and excise them, or he can excise a wedge of posterior vesical lip if there is a need for it. Following this both the posterior and the anterior incisions are closed by a transverse suture line to widen the vesical orifice.

We have used this operation in treating 8 children and have been impressed favorably with its value in these cases. They will be reported in some detail at a later date. The present report is concerned with the application of the operation to the treatment of bladder neck contracture in adults where its success may well depend on a principle which is entirely different from the original concept that was enunciated by Dr. Young. In contracture the entire outlet of the bladder is involved *in a dense scar. When the prostatic urethra is laid open anteriorly* by a longitudinal incision the ring of scar can easily be spread open by lateral retraction. Now the surgeon can determine by vision as well as palpation whether there is an elevated bar on the floor which needs excision. If present it can be removed by wedge incision and the defect closed with one or two interrupted sutures. But there may be no bar to excise at the posterior vesical lip. In either event it would appear that an essential principle is involved in the transverse closure of the anterior incision which incorporates a keystone of normal bladder muscle into the spread ring of scar. This should prevent further contracture.

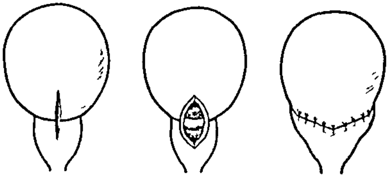

FIG. 1. Bradford Young's plastic technique for enlarging vesical orifice

A variant of this technique was recently reported in a personal communication by Mr. Noel Bonnin of Adelaide, South Australia. He uses a Y shaped incision with the long arm opening the prostatic urethra (fig. 2). The apex of the triangular bladder flap then slides down nicely into the widened urethral opening forming a V closure. Bonnin states that he utilized this procedure in a hemophiliac with prostatism in whom he feared to perform enucleative prostatectomy. He simply enlarged the bladder outlet as described and was able to control bleeding satisfactorily by careful suture. The patient had excellent urinary function after operation although none of his gland was removed.

We have used Bradford Young's technique in treating 14 adults, nine of whom had recurrent obstructions following previous operations. The remaining five had vesical neck contracture but had not previously been operated upon. It might well be argued that these 5 would have done just as well if treated by transurethral resection. However, three of them needed suprapubic drainage for atony of the bladder or for dilated ureters and kidneys so the plastic procedure seemed to be a logical addition to the operation.

The results have been gratifying in 13 of the 14 cases. One of the patients, a man with atony of the bladder, has not been benefited at all and is now on permanent suprapubic drainage. The result has been excellent in 9 cases while four have been significantly improved yet cannot be considered cured. One of the latter, however, comprises our most satisfying result. When this patient came to us he had been on suprapubic drainage for 7 years and had a bladder that contained many calculi. He told us that he had been operated upon in Germany by the suprapubic approach and was told that a cold punch was used. He urinated only once following operation so later another operation was performed with the same result. Our endoscopic examination revealed a tight contraction ring at the bladder neck which could be dilated by filiforms and followers so as to permit the introduction of a small resectoscope. Wide transurethral resection was performed and the stones were removed from the bladder. On the third postoperative day the suprapubic tube was clamped and he voided once, then no more. We looked into the urethra a few days later and found again that there was a tight contraction ring at the bladder neck which was resected with vigor and great enterprise in the hope of removing all the scar. Three days later he again voided once and that was all. We resigned ourselves to failure and gave up any thought of total perineal prostatectomy because the ureters were too close to the bladder neck to permit safe performance of the operation.

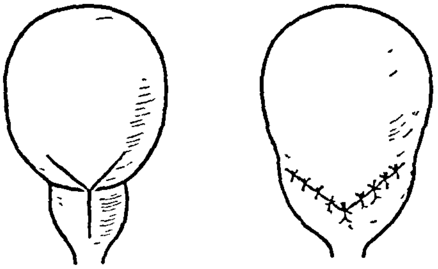

FIG. 2. Bonnin's Y-plasty for enlarging vesical orifice

The report of Dr. Young's operation held out the hope that the procedure might benefit this patient so he was called in and it was done. The immediate result was excellent, and within a month his urine was normal. He voids a full stream and has a normal bladder capacity but he has stress incontinence. However, this does not hinder him from earning a livelihood nor does it diminish his gratitude. This is the only patient among the 13 who has any incontinence.

Another case should be reported separately because of an unusual feature. This young man had 2 previous transurethral resections for vesical neck contracture and never was able to empty his bladder and voided with an interrupted stream. Endoscopy revealed an adequate bladder outlet. At operation the bladder outlet was large enough to easily accommodate the tip of the forefinger yet the entire bladder neck was a rigid cone of scar. The prostatic urethra was laid open with a vertical incision and the edges were widely separated. When the incision was closed transversely a broad flap of bladder muscle was brought down so as to become the anterior part of the bladder outlet. After operation this man voided with a large and uninterrupted stream and emptied his bladder.

In this case rigidity of the bladder neck may have interfered with normal micturition even though the caliber of the outlet was large.

Our observations thus far have made us feel enthusiastic about the procedure, and we commend it to others in the treatment of recurrent vesical neck contracture. It is hoped that the long term results will be as good as they now promise to be.

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YOUNG, B. W.: A retropubic approach to vesical neck obstruction in children. Surg., Gynec. & Obst., 96: 150-154, 1953.

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VESICOVAGINAL FISTULA: AN EFFECTIVE TECHNIQUE OF REPAIR

JAMES C. SARGENT*

In his monograph, *Gynecology, With a Section on Female Urology,* Wharton[1] has written "Fistulas are difficult to close. This is shown by the results that are obtained, for practically all cases have been operated upon many times." That Wharton's comment is a fair one seems amply borne out by the experience of the 18 women whose cases form the basis of this presentation. The records of fourteen of these patients tell of thirty-three unsuccessful transvaginal operations, a total of 5 attempts having been made in one of the cases. Besides the transvaginal surgery one patient had been operated on transvesically and in 2 patients there had been three attempts at closure by fulguration of the fistula. (*Judd[2] reported 44 cases having had 111 unsuccessful operations before being* registered at the Mayo Clinic.)

If such is anything like the common experience of women suffering with this terrible affliction, it is apparent that the whole subject warrants careful review. It is a tragedy of the first magnitude when a woman, usually a wife and in the very prime of her life, becomes a constant stinkpot through this misfortune. There are but few things more distressing that might befall her and when this unfortunate accident has occurred the dilemma in which her surgeon finds himself is indeed great. If only it were possible to dry things up again simply by a little freshening of tissue and a few stitches per vaginum! As one reads the literature, he can hardly escape the feeling that this very temptation to find a quick and easy way out of a most worrisome situation accounts, more than anything else, for the repeated failures and frustrations that are recorded.

Nor is it surprising that in searching the record, a variety of odd if not actually objectionable procedures are found to have been suggested. Special suture materials up to wire itself have been used as strong and lasting tension stitches. This, despite the fundamental principle governing all plastic surgery (and this is plastic surgery) that tension will always defeat healing. And many a poor woman has been made to lie prone on her belly for weeks—as if that would in some mysterious way keep urine from bathing the wound and prevent healing.

At this point I might digress to speak my confident belief that the woman with a vesicovaginal fistula is lucky indeed if she is to have her fistula repaired at the hands of a urologic surgeon. The reasons are several and quite obvious. To begin with, he did not cause the fistula so that he is not under any distracting embarrassment that might disturb his surgical judgment as to time and method of repair. Moreover he is completely at home in the operative field and he is quite familiar with both the anatomy and the surgical principles involved.

Despite the varied and somewhat confused literature on the subject of repair

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Read at annual meeting, American Association of Genito-Urinary Surgeons, Shawnee-on-Delaware, Pa. May 26–28, 1954.

* Deceased October 7, 1954.

[1] Wharton, Lawrence R.: Gynecology, With a Section on Female Urology. Philadelphia: W. B. Saunders Co., 1947, 331.

[2] Judd, E. S.: The operative treatment of vesicovaginal fistulae. Surg., Gynec. & Obst., 30: 447–453, 1920.

of a vesicovaginal fistula, there is considerable agreement upon certain principles that are important, even though some recommended techniques of closure do not always follow them. TeLinde[3] in the recent edition of his textbook, *Operative Gynecology,* lists a half-dozen principles some of which are of major importance. Deviating from his order I would put down as widely accepted: 1) a six months delay to allow softening of tissues; 2) preliminary cystoscopic study; 3) wide mobilization of layers to permit closure without tension; 4) closure in layers; 5) certainty of bladder drainage.

On the record alone, one cannot help but differ with him in his one added principle that "vesicovaginal fistulas should be closed per vaginum." Just to the contrary I would add a sixth principle to the effect that good exposure, better by far than that permitted working transvaginally, is essential to permit the precise surgery that is necessary for successful closure. And, even if implied in his others, a seventh principle should be carefully spelled out to the effect that the lining of the fistula, together with all heavily scarred surrounding tissue, must be removed.

With these as governing principles to be followed in the repair of a vesicovaginal fistula, I should like to describe a technique of closure that I adopted in 1934 and have since employed in eighteen women without failure except for one death from pulmonary embolism—in a patient, incidentally, who was operated upon years ago when this tragic complication was far more prevalent than today. And following essentially this same technique my colleague and associate, Dr. C. R. Marquardt[4] in 1946 reported an additional 4 cases that he had successfully repaired.

In this report no claim whatever is being made either as to originality or priority. Each of the several major elements in the technique to be discussed are well known and long since have been used in one way or another by many surgeons. A half century ago Trendelenburg first used the suprapubic approach. Professor Legueu[5] and a succession of others including Dr. Vincent J. O'Conor[6] have reported working transperitoneally, carrying a midline bladder incision down onto the fistula itself, and then separating bladder and vagina with great pains before excision and closure of the fistula. It is a combination of these basic techniques, modified but slightly here and there, that has prevailed in our experience and is proposed today as a perfectly safe procedure offering quite consistent cure of this miserable and too often badly handled problem.

Prior to incision, three very simple but very helpful things are done. Ureteral catheters are introduced cystoscopically. And since the leaking bladder cannot be distended, its easy identification is insured by the overexpanded bag of a Foley catheter. The vagina is then packed tightly with gauze. With the vagina thus packed and ureteral catheters in place, wide separation of the bladder floor from the anterior vaginal wall is made possible without danger of injuring the ureters or buttonholing the vagina.

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[3] TeLinde, Richard W.: Operative Gynecology. Philadelphia: J. B. Lippincott Co., 1953, p. 203.

[4] Marquardt, C. R.: Suprapubic repair of vesicovaginal fistula. Urol. & Cutan. Rev., 50: 6–8, 1946.

[5] Legueu, Felix: The transperitoneal closure of vesicovaginal fistulae. Surg., Gynec. & Obst., 48: 796, 1929.

[6] O'Conor, V. J. and Sokol, J. K.: Vesicovaginal fistula from the standpoint of the urologist. J. Urol., 66: 579, 1951.

Complete excision of the entire fistulous tract—mucous membrane, scar and all—must be accomplished and a good wide margin of healthy bladder floor must be dissected free from its vaginal attachment. Here as in all major surgery, especially when working deep and in the presence of some bleeding, excellent exposure is of utmost importance. It is in this regard that the vaginal approach is extremely inadequate and the simple transvesical approach but very little better. To reach the ultimate in good exposure we now employ the transverse suprapubic incision and then open the bladder high in its fundus carrying a midline incision all the way down to the fistula. To avoid the nuisance of incessant weeping of blood from the denuded bladder vault we prefer working transperitoneally though a number of bowel adhesions deep in the pelvis may make it advisable to extraperitonealize the bladder fundus in order to reflect the peritoneum and its loops of adherent bowel out of the operative field.

Not only lining mucosa but the devitalized scar tissue surrounding the fistula must be excised in order that good viable edges, when sutured together, may be expected to heal. And of equally great importance there must be ample separation of the bladder floor from the roof of the vagina to permit closing the defect in the bladder wall without the slightest tension. O'Conor[6] and others even have questioned the importance of suturing the vaginal opening if the bladder has been properly closed. To accomplish this wide excision of the fistulous opening and gain free mobilization of the bladder floor, the incision is extended down to and around the fistula, completely circumcising its orifice including a cuff of adjacent wall sufficient to reach perfectly healthy bladder mucosa and muscularis (fig. 1, *A*). With this accomplished the final steps in preparation for closure are simple. The cut edges of the bladder wall are undermined and freed widely from its attachment to the front of the vagina (fig. 1, *B*). The fistulous tract, still attached to the front vaginal wall, is then cut away down to its actual orifice in the vaginal mucosa.

The vagina and the bladder must be closed separately. In most cases the opening in the vagina is quite small and can be closed easily by a single purse-string stitch with mucous membrane inverted into the vaginal canal (fig. 1, *C*). If the opening is quite sizable requiring considerable suturing it is essential that the lateral vaginal walls be mobilized so that suturing can be done here too without the least tension. The now free and well mobilized edges of fresh cut bladder are closed by a simple running stitch from the depth of the bladder opening up to the fundus and around a small dePezzer catheter (fig. 1, *D*). While more recent experience has indicated there is little or no need for it, both Marquardt[4] and I have taken pains in earlier cases to interpose a flap of peritoneum between the closed bladder and vagina. Others have used an omental flap for this purpose. As a matter of fact, under the above procedures the point of closure of the vagina usually falls quite away from the line of suture in the bladder base and,

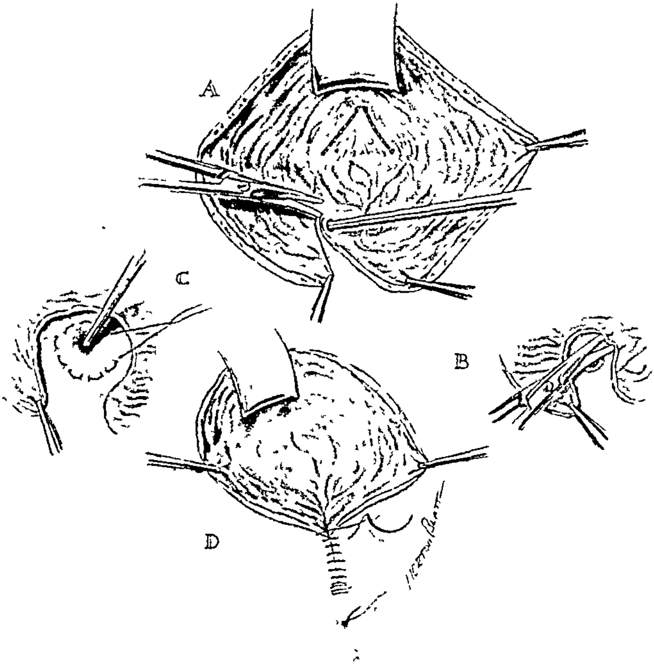

Fig 1

if not, one or two submucous sutures catching up the bladder muscle from side to side make a quite effective interposition.

Closure of peritoneum and belly wall are routine. The one remaining consideration is that of bladder drainage. This of course holds prime importance in the success of the procedure. As indicated earlier, the problem is hardly one of trying to keep the sutured inner surface of the bladder free from urine by special posture of the patient. It is simply one of avoiding accumulation of urine under the slightest pressure within the bladder cavity for the week or two necessary to permit firm healing of the bladder wall. This is so essential that for several days, perhaps a week, a small suprapubic dePezzer catheter is employed as double assurance in case the urethral catheter fails to function. Provided healthy viable bladder wall has been sutured and that without the slightest tension, the extra dePezzer can be removed after the first week and the urethral catheter the week following. By then the repaired fistula and usually the suprapubic wound will have healed tightly and normal voiding may be resumed.

RÉSUMÉ

A quite safe and very effective technique of repair of a vesicovaginal fistula is presented.

The importance of repair by one experienced in urologic surgery is stressed.

Successful repair is dependent upon strict adherence to several fundamental principles: good exposure; complete excision of the fistulous tract including its surrounding scar tissue; adequate mobilization of the free edges of bladder wall; closure of the vagina and bladder in layers and without the least tension; and careful postoperative bladder drainage for 2 weeks.

ADDENDUM

A color film of the last of these 18 patients was shown at the 1954 meeting of the American Urological Association in New York City and then at the 1954 meeting of the American Medical Association at San Francisco. The illustrations presented today have been sketched freehand from several frames of that film.

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CINEFLUOROGRAPHIC STUDIES OF BLADDER AND URETHRAL FUNCTION

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Many informative investigations and clinical studies have appeared in the literature concerning the mechanism of both normal and abnormal micturition, despite this, there still remain a number of problems to be studied A brief consideration of some of these investigations and clinical reports will permit one to better understand that further studies are indicated

From their studies on animals and humans, Langworthy, Kolb and Lewis[1] stated that " micturition is initiated by a contraction of the vesical muscle itself It is only after this contraction is well under way that the vesical orifice opens and then the external sphincter relaxes Neither can be opened voluntarily The vesical orifice opens following voluntary contraction of the detrusor It is possible to close the external sphincter, which leads to subsidence of vesical contraction The abdominal muscles have no power to initiate micturition except in cases where the activity of the vesical muscle is abnormal "

Muellner[2, 3, 4] and Muellner and Fleischner[5] who studied micturition fluoroscopically called attention to " the deliberate relaxation of the muscles of the pelvic floor which precipitates the reflexes of micturition, and the willful contraction of these muscles which cause cessation of the stream " This brings into consideration the role of the external sphincter in cessation of the urinary stream Muellner et al[5] also noted the change in bladder position during voiding and stopping, descending on voiding and ascending on stopping They also pointed out the important role of the pubococcygeus muscle in stopping and starting urination

Smith[6] demonstrated that the pubococcygeus muscle (fig 1) takes its origin from the pelvic surface of the body of the pubis and the superior rami The major portion of the muscle extends backward uniting with the ilio coccygeus

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Read at annual meeting American Association of Genito Urinary Surgeons, Shawnee on Delaware, Pa May 26–28, 1954

This study was supported with funds from the Department [illegible] lina Ritter Shumway Research Fund of the Department of Surge[illegible]

The early part of our studies was carried out with Dr Ra[illegible] Department of Radiology and the dog work was done by Dr Frank G Carpenter of the Department of Physiology We gratefully acknowledge the untiring technical help of Mr Karl Sutter

[1] Langworthy, O R, Kolb L C and Lewis L G Physiology of Micturition Baltimore Williams and Wilkins Co, 1940

[2] Muellner, S R The physiologic components of the urinary bladder New Eng J Med, **241** 769–772 1949

[3] Muellner, S R The physiology of micturition Its clinical application Bull New Eng Med Center, **12** 93 97, 1950

[4] Muellner, S R The etiology of stress incontinence Surg, Gynec & Obst, **88** 237–249, 1949

[5] Muellner, S R and Fleischner F G Normal and abnormal micturition A study of bladder behavior by means of the fluoroscope J Urol, **61** 233–243 1949

[6] Smith W C The levator ani muscle, its structure in man, and its comparative relationships Anat Rec, **26** 175–203, 1923

muscle across the midline between the anus and coccyx and is attached to the lower three or four coccygeal vertebrae. It is generally agreed in the female that the external sphincter is poorly developed and that the levator ani and in particular the pubococcygeus muscle, which is one component of the levator ani, have accessory sphincter action and are relaxed during active urination.

Young and Wesson[7, 8] concluded from their studies that the loops of the longitudinal and circular muscles of the bladder itself converge to form the internal sphincter at the bladder neck; however, as such, there is no marked muscular development at this site as pointed out by Griffiths,[9] and others. Huggins et al.[10, 11] found in the male dog that the membranous urethra is surrounded by striated muscle from the apex of the prostate to the pelvic diaphragm, while in the female dog the comparable part of the urethra is surrounded by smooth muscle; and voluntary muscle is concentrated as a band around and near the external urethral meatus.

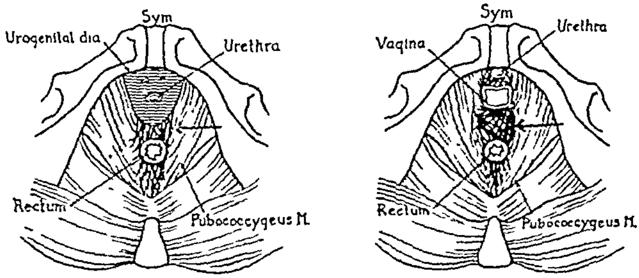

FIG. 1. Diagrams of relationship of pubococcygeus muscle to urethra in male and female. Note interdigitation of fibers of pubococcygeus muscle about urethra (arrow). Abbreviation: Sym.—symphysis pubis; dia.—diaphragm.

Since cinefluorographic equipment is available in our Medical Center, it was thought worthwhile to determine what further information might be acquired concerning the mechanism of urination by the use of this equipment; and with this in mind, the following preliminary work was carried out on 7 dogs and 37 patients.

TECHNIQUE

All of the examinations were recorded on 35 mm. film at camera speeds of 7½ or 15 individual negatives per second. Henceforth the individual negatives will be referred to as frames. Average x-ray factors were 75 m.a., 125 KVP, with added filtration of 1 mm. aluminum. Average scene length was 20 seconds, often interrupted several times, depending upon the varying problems of the individual examination. Average x-ray dosage per examination was 2 r per second

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[7] Young, H. H. and Davis, D. M.: Young's Practice of Urology. Philadelphia: W. B. Saunders Co., 1926, vol. 1, chapt. 1, p. 5.

[8] Wesson, M. B.: Anatomic, embryological and physiological studies of the trigone and the neck of the bladder. J. Urol., 4: 279–315, 1920.

[9] Griffiths, J.: Observations on the urinary bladder and diverticulum. J. Anat. and Physiol., **29**: 61–83 and 254–275, 1894–95.

[10] Huggins, C. B., Raymond, H. E. and McCarroll, H. R.: Urethral clonus; a contribution to the physiology of ejaculation. J. Physiol., **108**: 192–196, 1934.

[11] Huggins, Charles, Walker, A. E. and Noonan, W. J.: Sympathetic and pudendal nervectomy for vesical atony. J. Urol., **41**: 696–714, 1949.

measured at the near point of the skin Most of the subjects were males over fifty years of age Several younger men with terminal malignancies were examined as well as several women with bilateral oophorectomies Satisfactory pictures were made on individuals weighing 150 pounds or less, and excellent pictures were easily obtained upon patients weighing 125 pounds or less The cinefluorographic and photographic equipment have been described elsewhere by Ramsey et al[12]

The patient was prepared in the following manner The penis was carefully cleaned with soap and water and a 16F soft rubber catheter passed per urethram, and the bladder filled with a solution of 30 per cent urokon* using a large bulb syringe As soon as the subject felt a desire to urinate the catheter was removed Generally we have used 200 to 400 cc of 30 per cent urokon to elicit a desire to void The patient was usually permitted to rest a few minutes, depending on the type or phase of micturition to be studied He was then placed between the x-ray tube and fluorescent screen in a position chosen by fluoroscopy to demonstrate the region to be studied, and the scene run for the predetermined time Instructions were carefully given to the patient as to what he was to do, such as stop or start, or hold the urine, or strain to empty his bladder Since only short exposures were possible (around 20 seconds) it was imperative that all time be used to the best advantage during the filming of urination

The x-ray motion picture has a number of advantages in regard to the study of the micturition mechanism One can observe the frames in continuous motion as well as by individual frames and also by reversing the film Furthermore, loops can be prepared and these can be projected and repeatedly studied as indicated With the development of a new slow motion projector in the Department of Radiology any desired speed can now be attained which will permit observations of bladder and urethral function

MATERIAL

Before studying patients it was deemed important to gather information on this subject by studying dogs Seven dogs under intravenous nembutal anesthesia were studied under varying conditions We particularly studied urination in the normal male and female dog

In order not to disturb or traumatize the urethra and bladder, we exposed the kidney through a flank incision and passed a 4F ureteral catheter from the renal pelvis, *down the ureter and into the bladder lumen (fig 2)* *This technique* also permitted the bladder to be filled at a distance from the source of radiation and hence reduced radiation hazards to the investigators

The 30 per cent urokon was then instilled by gravity flow and as soon as urine was seen at the meatus the x-ray motion picture was started We discovered that the induction of a little air into the bladder through the catheter would initiate urination, and since it took, at times, large volumes of contrast medium to initiate urination in the dog, we adopted the use of air to start urination after using around 150 to 200 cc of 30 per cent urokon.

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[12] Ramsay, G H S Watson, J S , Jr , Steinhausen, T B , Thompson, J J , Dreisinger, and Weinberg S Cinefluorography Radiology, 52. 684 690, 1949

[*] Urokon was generously supplied by Mallinckrodt Chemical Works of St Louis, Missouri

Urination was already in progress when filming began in all of the dogs studied and subsequently no changes were noted at the bladder neck. However, one can plainly see the external sphincter open and close. In one male dog the pudendal nerves were approached through a perineal incision and both were severed high. This procedure resulted in the disappearance of the previously observed sphincter action.

In the female dogs the urination was also in progress when filming began in all cases studied and the bladder neck was open and similar to that viewed in the males. No changes were seen in the region of the bladder neck as the stream shut off and started again. The sphincter action near the urethral meatus is very clearly seen and confirms the findings of Huggins et al.[10] In no instance were we able to obtain complete emptying of the bladder in the dog. In one female dog we cut the left presacral nerve and it appeared that the left bladder wall might be somewhat atonic but further work is necessary to confirm this observation.

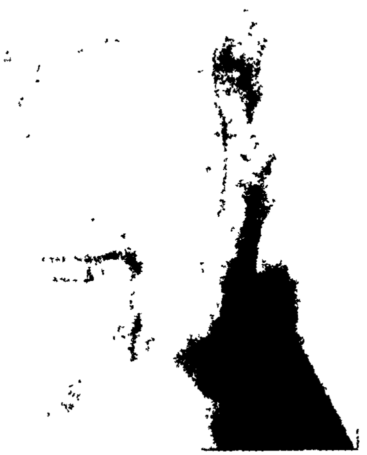

FIG. 2. Enlargement from motion picture film of dog's bladder. Bladder has been inflated with air by means of catheter inserted through one of the ureters.

In our studies we elected to use patients over 50 years of age because of possible radiation hazard to the gonads. Total radiation did not exceed 50 r to any one individual. In 2 cases we used patients under 50 years of age with incurable malignant disease not related to the urinary tract. Most of the patients had benign prostatic hyperplasia with minimal urinary symptoms, and they were used mainly as controls so that their findings could be compared to those seen after various types of prostatic surgery.

CASE REPORTS

Case 1. H. P., R. M. H. No. 121264, was a 44 year old man with moderately advanced Hodgkin's disease and no apparent urinary symptoms or difficulty on urination. Cystoscopic study did reveal, however, a median bar at the bladder neck and diverticula. In figure 3 one can observe steps in the act of starting and stopping the urinary stream. Steps 5 to 8 represent successive frames and a total time of $\frac{1}{5}$ of a second. As Muellner et al.[5] pointed out in their fluoroscopic studies, the position of the bladder changes with starting and stopping of the urinary stream. Figure 4, *A* shows the bladder and urethra during urination, at which time the base of the bladder is shaped like a cone. In figure 4, *B* immediately after urination has been interrupted at the external sphincter, the base of the bladder is seen to be elevated and is now more rounded than conical. The prostatic urethra is distended. A more complete picture of the action is shown in figure 3.

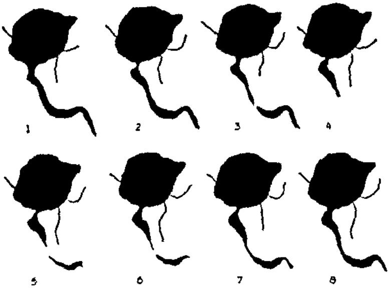

Fig. 3. Tracings from film of case 1. Steps 5 to 8 are tracings from consecutive frames made at a speed of 15 frames per second (total time for these steps is $\frac{1}{5}$ of a second).

It should be noted that the segment of the urethra which becomes obliterated during contraction of the external sphincter is of considerable length. One might suspect that if the external sphincter alone were acting, the region of shut off, which is free of contrast medium, would be more confined or more focused to a ring-like constriction. Furthermore some data can now be gathered with considerable precision in regard to the time it takes to start and stop as quickly as verbal instructions can be given to a co-operative and understanding patient. In figure 3 from step 3 to step 8 it takes $\frac{1}{5}$ of a second. It is also demonstrated that once the bladder neck opens to permit urine to enter the prostatic urethra, even though the patient stops and starts, the bladder neck does not close again; the shut off of the stream is seen to be in the region of the external sphincter, proximal to the bulbous urethra.

Case 2. H. H., R. M. H. No. 249228, shows vesico-ureteral reflux in a patient aged 72 years with benign prostatic hyperplasia and some decrease in the strength and size of the urinary stream and occasional nocturia. In figure 5 the patient is actively voiding and the contrast medium can be seen in both ureters (arrow). In the x-ray motion picture of this patient the peristaltic waves can be clearly seen passing down the left ureter while the patient is voiding. One could explain on this basis the manner in which infection might reach the upper tract by way

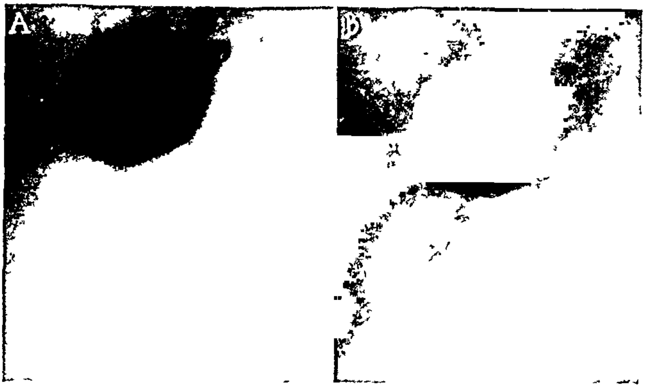

FIG. 4. Bladder and urethra, male aged 50. *A*, subject voiding. *B*, voiding stopped by voluntary contraction of external sphincter. Arrow points to segment of prostatic urethra which dilates with urine when external sphincter closes.

of the column of urine. This observation helps to support the findings of Weyrauch.[13]

Case 3. M. R., R. M. H. No. 18668, aged 67 years, underwent suprapubic prostatectomy for benign prostatic hyperplasia, and 7 months later the x-ray motion pictures were made. In figure 6, *A* the patient is voiding, and one's attention is attracted to the part of the urethra between the bladder neck and the prostatic fossa. This portion of the urethra shortens when the patient stops (fig. 6, *B*). Furthermore, the fossa moves upward with the ascending bladder when urination stops, and the base of the bladder flattens. The contrast medium is seen to disappear completely from the urethra distal to the prostatic fossa. In the x-ray motion picture itself the bladder emptied, and on checking with a catheter after voiding we found no residual urine. It is of interest to note that there is an even and symmetrical contraction of the bladder while urination is in progress, even though the approach was by way of the suprapubic region and a sinus existed for a short time between the bladder itself and the skin. Apparently what fibrosis might be present after healing does not impede the bladder, sphincter, or urethral function. Of course, every attempt is made to preserve sphincter competency regardless of the type of prostatic surgery carried out.

Case 4. J. J., S. M. H. No. 363572, aged 66, underwent retropubic prostatectomy for benign prostatic hyperplasia. The x-ray motion pictures were made 2 months after this procedure and showed particularly well the segment of the urethra between bladder neck and prostatic fossa which was referred to in case 3 after suprapubic prostatectomy. The question has arisen whether part of this segment is produced by the thickness of the bladder wall. During urination (fig. 7, *A*) the urethra and fossa are well outlined by contrast medium and the urethra is widely open. On stopping the urinary stream (fig. 7, *B*) the contrast medium appears to terminate at the distal end of the fossa in the region of the external sphincter; furthermore, no contrast medium is seen beyond the fossa when the urinary stream is shut off. This patient emptied his bladder completely as demon-

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[13] Weyrauch, Henry M. and Bassett, J. Brandon: Ascending infection in artificial urinary tract: An experimental study. Stanford Med. Bull., 9: 25–29, 1951.

FIG 5 Bladder of case 2 Reflux of contrast medium up both ureters is indicated by arrows In motion picture a peristaltic wave can be seen progressing down left ureter during active urination

strated in the movies and also as determined by passing a catheter for residual urine

Case 5 L W, S M H No 272660, and *case 6*, E P, S M H No 361798, represent 2 interesting patients with outpouching of the bladder Case 5 is a 55 year old man with a history of painless hematuria on one occasion and some vague discomfort deep in the right lower abdomen near the midline It appeared that the discomfort was lessened by urination In the x-ray motion record one sees a single definite outpouching (fig 8, *A*) After urination is well on its way (fig 8, *C*) we observed that the outpouching has disappeared, and the x-ray motion picture shows that his bladder has been emptied of contrast medium

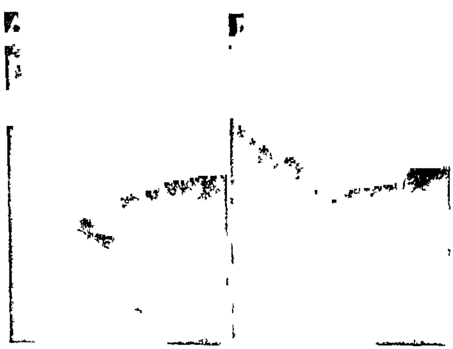

FIG 6 Case 3 Sixty seven year old man 7 months after suprapubic prostatectomy *A*, during voiding *B*, cessation of voiding Note that prostatic fossa has moved up with bladder

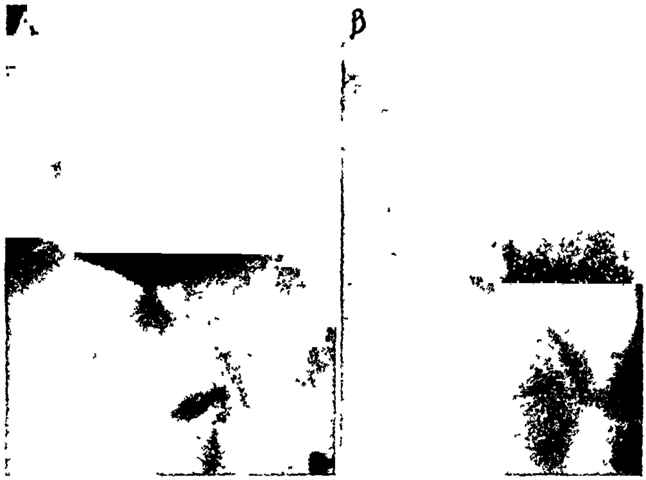

FIG. 7. Case 4. Sixty-six year old man 2 months after retropubic prostatectomy. *A*, full urination. *B*, after shut off urinary stream. Observe that prostatic fossa is elevated, as in case 3.

There is no evidence of any residual contrast medium to identify the site of the outpouching. *Case 6*, E. P., S. M. H. No. 361798, a 54 year old woman, with bilateral oophorectomy and E. coli cystitis, had a very definite tenderness on vaginal examination in the region of the right side of the bladder floor. In the motion picture one sees a similar outpouching of the bladder as that described in case 5. We also studied this patient by movies in the supine position and the outpouching did not show, but a small spot of contrast medium could be seen to follow the great mass of medium in the bladder proper, and on emptying this spot was visible near midline. In upright position the outpouching was clearly visible. This outpouching, like the one described in case 5, also emptied on urina-

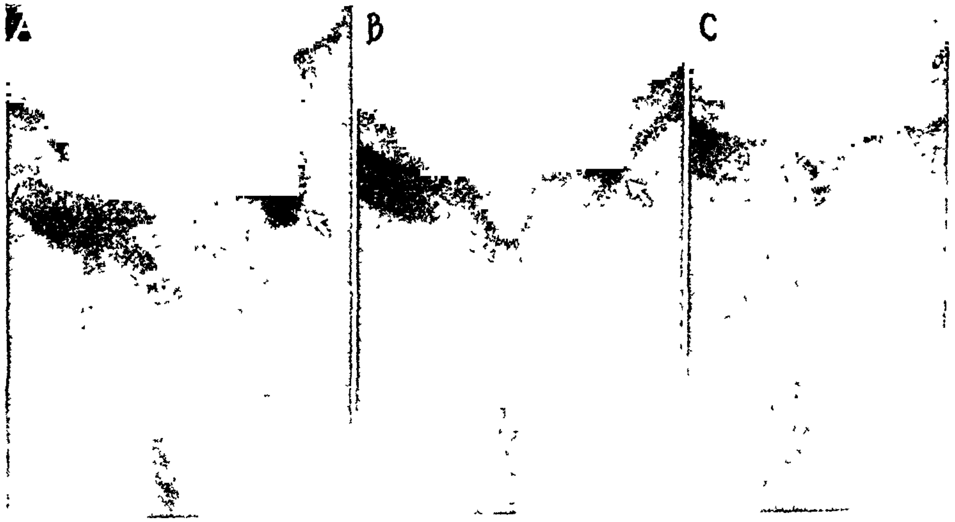

FIG. 8. Three stages of urination in case 5. *A*, outpouching (arrow). *B*, decrease in size of outpouching (arrow). *C*, outpouching disappears as urination continues. Double line in region of prostatic urethra is produced by margin of symphysis pubis.

tion. The right side of the bladder was resected with complete relief of pain and the infection disappeared. In the x-ray motion picture after surgery, the outpouching was not visualized and the bladder was symmetrical and complete emptying as demonstrated by movies. Catheterization demonstrated no residual urine. It seems reasonable to believe that the outpouchings described in the above 2 patients have muscle in them since they contract along with the bladder muscle itself during micturition.

In *case* 7, J. R., R. M. H. No. 179650, a man aged 55, we used successive intravenous injections of 70 per cent urokon (without catheterization) and demonstrated contrast medium in the bladder. The procedure was as follows: 15 cc of 70 per cent urokon were given intravenously and this was repeated 20 minutes later. We observed the bladder region under the fluoroscope until we visualized the bladder and then took our movies during stopping and starting. The bladder shadow on the x-ray motion picture is fair but the urethral outline is poor. We collected the urine to determine the per cent of medium in the bladder urine which was found to be about 6 per cent. Urokon is excreted slowly as pointed out by Neuhaus et al.[14] and it might be well to wait for a much longer period of time and then, perhaps, better concentration in the bladder would produce a better shadow and permit improved x-ray motion picture visualization of the medium during stopping and starting. In the future this method might become clinically useful and eliminate any disdavantage of catheterization.

DISCUSSION

Cinefluorography has the advantage over fluoroscopic observations and the still x-ray film of cysto-urethrography in that it provides both a continuous motion and a permanent record. This is of great help when one deals with a number of events that come in close sequence. It is quite possible that during continuous motion some changes might be detected that otherwise might go unnoticed on the motionless x-ray film.

Muellner, who has made many notable contributions to our knowledge of the mechanism of micturition, observed fluoroscopically that, when a patient shuts off the urinary stream, the bladder rises; and with the resumption of urination, the bladder descends. He reported that the inhibition of the urinary stream appeared to occur at the level of the internal sphincter. We observed from our preliminary cinefluorographic studies of the individual frames as well as from frames in continuous motion, that if the bladder neck is once opened to permit urine and contrast medium to enter the urethra adjacent to the bladder neck, even though the patient stops and starts, the bladder neck does not close again; the shut off of the stream is seen to be in the region of the external sphincter, proximal to the bulbous urethra. The shut off taking place in the region of the external sphincter may well be aided by the pubococcygeus muscle as previously stated. In this instance the contrast medium is seen in the prostatic urethra of the male and is continuous through the bladder neck with the contents of the bladder cavity. In the 37 patients studied, we did not once see a shut off at the level of the bladder neck, provided the patient had started the stream and it had entered the prostatic urethra or the portion of the urethra nearest the bladder neck as in the female. However, as pointed out by Muellner et al.,[3, 5] the bladder neck (internal sphincter) was closed in the resting bladder and the bladder base under these conditions was more or less flattened out as compared to the more cone-shaped base of active urination.

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The photographs in this paper made from the individual frames comprising the x-ray motion picture itself do not do justice to the frames in motion. Furthermore, one might object to the poor quality of the photographs reproduced herein but it is to be remembered that these are unretouched. The value of both the still frames and the frames in motion is that one will have a record of the sequence of events in the micturition mechanism which, at present, is not obtainable by other methods in current use. An example of the usefulness of cinefluorography was seen in case 6, in which we found a little retention of the contrast medium during urination in the supine position. However, in upright position this little spot of contrast medium became an outpouching similar to that seen in figure 8, *A*. *During active urination the outpouching disappeared* as the bladder emptied. Furthermore, prior to filming the scenes we could observe this outpouching on the fluoroscopic screen, and if desired one could obtain a cysto-urethrogram.

Muellner observed also that, as urination starts, the vertical diameter of the bladder becomes larger while the horizontal becomes smaller. We observed this in one patient to a very marked degree, but generally speaking, as can be seen in the motion pictures, the individual bladder pattern for contraction varied considerably, and in most instances as one studied the motion records there was even symmetrical contraction of the bladder muscle. Furthermore the degree of descent on voiding and ascent on shut off varied considerably from individual to individual.

The influence of catheterization on the mechanism of micturition is apparently not marked. In one patient to whom we gave successive intravenous injections of 70 per cent urokon, we obtained a good bladder shadow with 6 per cent urokon that could be recorded on the x-ray motion picture film, and it was demonstrated that the same sequence of events takes place in essentially the same manner as that seen after urethral catheterization. Naturally more work of this type is planned. It is quite possible that x-ray motion record in the study of bladder and urethral function, and perhaps ureteral function, might be obtained in thin individuals by successive intravenous injections of 70 per cent urokon. Furthermore, it is hoped that the use of the image intensification tube will permit the taking of longer scenes with oblique views and with much less radiation and probably better definition of the structures being filmed.

A number of problems could be studied by this method such as incontinence after various types of prostatic surgery, the problem of stress incontinence which is ever before the gynecologist and urologist alike, and neurological disorders involving the bladder and urethra.

We also believe that the field of vesico-ureteral reflux which has been so ably studied by Stewart,[15] Bunge,[16] and others, can now be investigated with the cinefluorography in view of the findings in case 2 (fig. 5). With the use of the image intensification tube the investigation of vesico-ureteral reflux in children becomes possible. Thus we may note from the foregoing findings that cinefluorography may have a number of very useful applications in the fields of clinical and experimental physiological Urology.

SUMMARY

In our cinefluorographic observations of the bladder and bladder neck in 37 patients, the neck was closed and the base more or less flattened during the inactive or resting phase before urination. During the active phase of urination the bladder descended and the base became cone-shaped. Subsequently, on stopping the urinary stream, the cut off was always seen to take place at the level of the external sphincter.

The segment of urethra obliterated in the region of the external sphincter appeared quite long. We agree with Muellner and others that it is likely that the pubococcygeus muscle has an integral role in the shut off mechanism.

It appears from our studies that cinefluorography will provide a tool with which to study such problems as stress incontinence, incontinence after various types of bladder and prostatic surgery, bladder disorders associated with neurological disease, and other conditions related to bladder and urethral functions. In addition, an x-ray motion record of physiological experimental work on the urinary tract can be obtained for study at the convenience of the investigator.

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ABACTERIAL URETHRITIS, ABACTERIAL PYURIA AND REITER'S SYNDROME

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Thirty-eight years ago, Reiter studied and described a case of urethritis, conjunctivitis and arthritis, not gonococcal in origin, which has been known since as Reiter's syndrome. As time has gone by, many reports of similar cases have appeared in the literature and our attention has been frequently called to the fact that others simulating this disease presented either urethritis and arthritis, or urethritis and conjunctivitis, accompanied by skin, preputial, mouth or eye lesions. Abacterial pyuria, as well, has likewise been brought before us evidencing certain characteristics pertaining rather to those of the so-called Reiter's syndrome. Much as been published in relation to these two entities, but careful analysis will no doubt show that urethritis has been manifest in a great percentage of them.

During the past 9 years we have had the opportunity of observing three typical cases of Reiter's syndrome; three others, in which one of the components of the triad was absent; two of abacterial pyruria and still eighteen more of what we called abacterial urethritis, for their complaint at consultation was a simple urethral discharge that presented no organisms. All patients were male and only one Negro. In all, there was a history of coitus eight to twenty days before the appearance of the initial urethral manifestation, although our first examination did not always coincide with the onset of the same. Those of Reiter's syndrome, prior to the onset of the joint and eye lesions, gave a history of having suffered in the past, for two to four years, repeated episodes of urethritis which disappeared, spontaneously, within two or three weeks. This was also true of those in which one of the triad components was absent. The purely urethritic cases were of recent onset and many had never, previously, complained of any urethral manifestation, and consulted us because of a persistent discharge in spite of former treatments with penicillin, sulfas and other antibiotics, which were of no avail. In many instances the discharge, as well as the frequency, burning and occasional hematuria, had been made even worse by the use of the antibiotics.

The discharges have varied in aspect, being at times grayish and mucopurulent and others, definitely purulent and yellow. Those belonging to the first type were accompanied by burning and frequency, but no particular loss of weight; the purulent ones, in contrast, had more marked manifestations of frequency, urgency, dysuria, extreme burning, nocturia, occasional hematuria and, quite often, loss of sleep and weight. Ill nourished individuals with lessened physical resistance presented more severe symptoms than the robust ones.

It is relevant to emphasize the fact that these patients have been seen during the months of March to mid-November, with only a sporadic one between the middle of November to March, but even this one claimed that his initial symptomatology started within the first mentioned interval; which makes us stop

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Read at annual meeting, Southeastern Section of American Urological Association, Palm Beach, Fla. April 12–15, 1954.

and wonder if this manifest periodicity of occurrence may not, in some way, be related to the unproven etiology of Reiter's disease.

The multiplicity of accompanying lesions observed in relation to these conditions varies from superficial erythematous manifestations of the preputial mucosa and skin to superficial ulcerations of the preputial mucosa and glans penis, violet-colored lesions of the palate, keratitis, iritis, conjunctivitis, arthritic and even extensive and generalized skin lesions, similar to psoriasis in aspect. In fact, one of our patients had undergone treatment without improvement for such an ailment and was referred to us because of the accompanying urinary symptomatology already mentioned. It was noted that each skin lesion, consisted, in its beginning, of a tiny, purulent accumulation around a hair follicle which, lasting for 24 hours, disappeared to give way to a very small, pinkish-red, and at first slightly elevated, erythematous lesion with reddish border, without scales, at times confluent, which gradually grew varied in size, forming then thick scales of grayish color. The glans penis was also covered by a thin scaly lesion which pealed off readily.

Another patient was referred because of a persistent conjunctivitis and iritis limited to one eye only, its vision progressively going from bad to worse in spite of opthalmologic treatment, and whose history revealed he had suffered, on and off for two years previously, spontaneously disappearing urethritis.

In the great majority we have noticed a definite, circumscribed, reddened and edematous meatal orifice lesion, and there has been present, in all, a generalized, discrete adenitis, which in itself suggests a systemic invasion, probably by way of the lymphatics, which might explain the observed multiplicity of lesions. Clinically, we consider these two manifestations most characteristic and of great help from the standpoint of diagnosis.

Cystoscopy must be carried out under anesthesia, particularly if the symptomatology has persisted for some time because, otherwise, the discomfort and pain caused by the presence of the instrument, plus the distention produced by the irrigating fluid, will often force us to discontinue it. In all three diseases the cystoscopic picture is the same and, to my interpretation, of diagnostic importance. The degree of inflammation and invasion of both vesical mucosa and prostatic urethra, as well as the diminution of vesical capacity, depend on the duration or acuteness of the episode.

A reddish-violet hued bladder mucosa, with little edema and mild inflammatory invasion of the neck, trigone and prostatic urethra, is noted when cystoscopy is performed immediately after the appearance of the exudate. Ten days to two weeks after the initiation of the symptoms we find, however, that not only are the inflammatory changes more intense but they may, in extension, surpass the trigone, involve the ureteral orifices and often go beyond, affecting the rest of the mucosa, in which case the bladder capacity will then be notably diminished and as a result, the mucous membrane bleeds easily if unduly distended. Catheterized specimens of urine from the kidneys will not show any bacteria.

Following cystoscopy there have been no thermic reactions of any sort, in spite of the existing purulent exudates, urethral and vesical mucosal inflammatory lesions and of the prostate, at times, which makes this a curious observation.

Cases of abacterial pyuria with unilateral hydronephrosis, urethral and vesical mucosal inflammation, edema and diminution of bladder capacity, plus others with bilateral hydronephrosis and hydro-ureters, have been reported. In many, nevertheless, hydronephrosis had not been demonstrated and we have only observed it in one instance so, naturally, since this happens in some but not in all, we wonder what may be the mechanism involved in its development.

The following facts stand out from the careful study of the films obtained in the hydronephrotic ones. The pelves and calyces are dilated, though the latter ones do not greatly change their normal contour; the ureter is also dilated and, often, presents marked narrowing of its inferior portion as it enters the bladder; this being, perhaps, the reason for so many reports pointing out the fact that, in such cases, catheters cannot be passed to the renal pelves. Furthermore, since wide meatotomy had to be carried out (biopsies later reported as leukoplakia) in 2 patients with abacterial urethritis—for cicatricial stenosis and thickening of the urethral meatus—because of their inability to void, we venture to point out the possibility that, in the aforementioned cases of abacterial pyuria with hydronephrosis, narrowing of the ureteral orifices may be caused by the same mechanism responsible for the meatal stenosis in those of abacterial urethritis. Thus, in those cases that develop narrowing of the ureteral orifices, intramural ureteral edema, diffused cystitis and lessened bladder capacity the patients will have, in our belief, a greater tendency to the development of hydronephrosis and hydroureter than those in whom the mucosal invasion does not go beyond the inner limits of the trigone. This interpretation may be of significance, when one considers that, occasionally, as has been reported, nephrostomy and even uretero-intestinal anastomosis have been resorted to, in order to alleviate these patients.

Because of the serious renal complications, disabling manifestation of arthritis, eye lesions, progressive depauperation and physical inability that some of these individuals present, I wish to stress a few simple concepts that may be of help, in diagnosis, from a practical standpoint, so that adequate and early treatment may be instituted.

We must keep clearly in mind that a most detailed history should be taken, with particular reference to previous self-limiting attacks of urethritis, eye, joint, meatal or preputial manifestations, whenever a case of abacterial urethritis is suspected, for this seems to be the starting point of all three conditions. The inspection of the urethral meatus is of special interest, for its characteristic appearance cannot be confused. Look for a discrete adenitis, which later becomes generalized but is first noticed in the inguinal and femoral regions; insist, besides, on performing cystoscopy, for its typical picture is of easy interpretation and, therefore, of value.

Many of these patients, as we have already mentioned, had undergone various antibiotic treatments, prior to our investigations, always without evidence of positive results. We have, instead, simply administered mapharcide, in doses of 0.06 gm. every fifth day, totaling ten to fifteen, together with polyvitamins and ample dietary regimen, with surprising and definite results, observed, often enough, shortly after its institution. The decrease in the exudate, ocular, arthritic, meatal and preputial lesions, together with the notable amelioration of pain, frequency and burning on urination, have, from the start, been remarkable. Finally, the confirmed improvement of their appetite, physical aspect and well-being, plus the gradual disappearance of all manifestations, including the adenitis, until recuperation, should in themselves, be ample demonstration of its efficiency; considering that all the patients, as of today, apparently have remained cured.

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TRANSPOSITION OF THE PENIS AND SCROTUM: CASE REPORT

DANIEL B. McILVOY and HENRY S. HARRIS

Transposition of penis and scrotum, sometimes referred to as marsupial type of genitalia, has been described in the literature eight times. Repair of this defect has been reported only once.

Hinman in his textbook of Urology mentions one case in a stillborn. He reports another that grew to manhood with good function of the penis which was located between the scrotum and anus.

Hontain reports in the Spanish medical literature a case of transposition of the penis and scrotum.

Segal reported a double parasitic monster with multiple congenital defects including prepenile scrotum, absence of one kidney and adrenal gland. The infant lived only 2 months.

Francis reported a case that lived only a few minutes after birth and was found to have a complete absence of the urinary tract. He mentions another case reported in the German literature as living and apparently healthy at several months of age.

Huffman reported a case that lived only 19 days after birth and had anomalies of the upper urinary tract with ureters probably emptying into the bowel.

Campbell reports an 11 month old boy described as having a penis dangling from his perineum behind a partially bifid scrotum. The child had no other congenital anomalies and correction was carried out by splitting the scrotal skin and bringing the penis anteriorly into normal position.

We wish to report an additional case of transposition of the penis and scrotum in a child who also had urinary obstruction due to a diverticulum of the prostatic urethra. Reconstruction of the urinary tract was successfully carried out.

CASE REPORT

H. L. M. (Hospital Registry No. 1292) was a 10 month old Negro boy first admitted to the hospital with a marked distention of the bladder, temperature 103F, and a congenital deformity of the penis since birth. The mother stated the child had had frequent attacks of fever and swelling of the lower abdomen. The urine had never come out in a definite stream but passed out through the penis constantly in a drip. Other than for moderate constipation the child had developed normally. Examination disclosed that there was transposition of the penis and scrotum (fig. 1). The scrotal contents appeared normal and in normal position but the penis was noted to hang from the anterior anal wall and directed in a downward and slightly backward position. The organ was of very small caliber but about 8 cm. in length. The urethra would admit no larger than an 8F ureteral catheter. Urine (500 cc) was drained out of the bladder and diodrast injected for cystography (fig. 2). There was no evidence of reflux of the dye into the ureters. Under vinethene anesthesia a suprapubic cystotomy was

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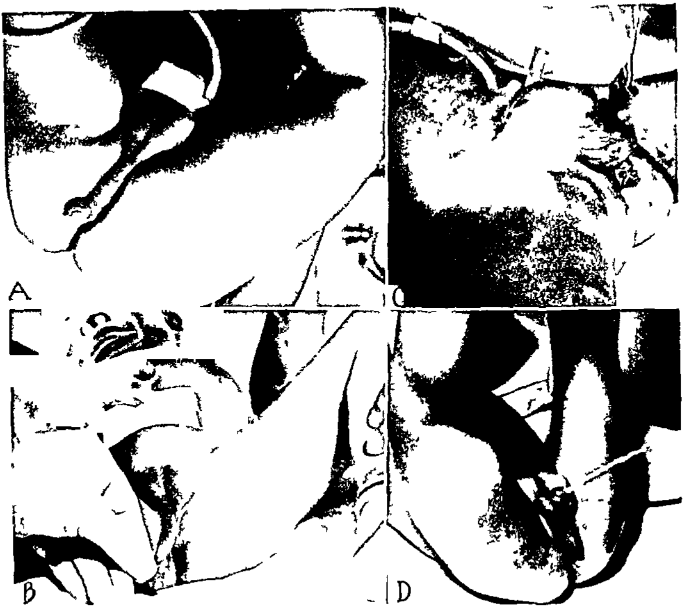

FIG 1 *A*, photograph of patient with transposition of penis and scrotum following suprapubic cystotomy but prior to repair *B*, showing reversed position of penis and scrotum Penis directed backward over anus *C*, photograph taken day of operation showing plastic tube in urethra and penis pulled through scrotum *D*, child voiding 6 weeks after repair Suprapubic tube still in place

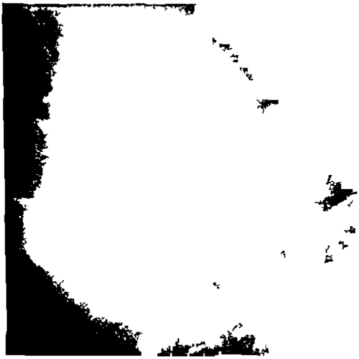

FIG 2 Cystogram and urethrogram showing diverticulum in prostatic urethra obstructing urinary flow

done and a 16 Foley catheter left in the bladder for drainage. The child did well following operation; the temperature fell to normal; and he was discharged to be followed as an outpatient with a suprapubic tube in place (fig. 1).

Following the first admission the child did well, gained weight, and developed normally. Several attempts were made to dilate the urethra but without success. It was felt that usually the filliforms could not be passed into the bladder. The child was re-admitted to the hospital at the age of 22 months and appeared to be in excellent health. The suprapubic tube was draining well. He was able to void very small amounts through the urethra and continued to have a residual urine of 150 cc. An attempt was made to pass an infant cystoscope through the urethra under vinethene anesthesia. The instrument would not pass by the prostatic urethra. The suprapubic tube was removed and a cystoscope was passed through the opening into the bladder and view of the bladder obtained. It was noted that the bladder was large and atonic, there being a rather deep pocket below the level of the urethra. X-rays revealed a large diverticulum (approximately 2 cm. in diameter) of the prostatic urethra situated on the anterior wall. After considerable manipulation it was decided that the child should be discharged to await further definitive treatment when the effects of the trauma to the urethra had subsided.

He was again followed as an outpatient. It was found that urine drained well through the suprapubic tube but only a few drops at a time were voided through the penis. The child was admitted to the hospital a third time at the age of 28 months. With the patient under a general anesthetic, a transverse incision was made just above the symphysis pubis and both recti muscles detached from the symphysis. The transversalis fascia and fat over the prostate were carefully wiped away. A longitudinal incision over the lower portion of the bladder was made. Traction sutures were attached to the wall of the bladder with elevation into the wound. A small curved hemostat was passed through the neck of the bladder into the prostatic urethra. The blades of the hemostat were opened and an incision made through the anterior wall of the prostate into the diverticulum of the urethra. This diverticulum was found to be smooth and contain a curled up filiform which had been passed through the penis just prior to the operation. The urethra was dilated up to 14F after meatotomy was done. A polyethelene tube of that size was passed through the urethra to the bladder. The end in the bladder was secured to a Malecot suprapubic catheter with stainless steel wire which protruded out through the lumen of the catheter to prevent its slipping out of the urethra before healing had occurred. The wall of the bladder and the prostatic urethra were closed with interrupted chromic 000. A drain was placed in the space of Retzius. The rectus muscles were re-attached to the symphysis pubis and the skin was closed with interrupted catgut. The penis was dissected away from the anal canal by making an incision around the complete circumference of the penis at its junction with the anal canal. A stab wound was made through the inferior portion of the scrotum and a second one through the superior portion. The penis, including the polyethelene tube, was passed through a tunnel made from one of these stab wounds to the other. The skin at the base of the penis was sutured to the lower portion of the scrotum while the skin in the distal portion of the penis was sutured to the skin at the upper margin of the scrotum. Small tissue drains were placed near the suture line. It was with considerable difficulty that the posteriorly curved urethra was mobilized and placed into the usual normal anterior curve. The wound healed without infection and the child was dismissed from the hospital with the tube in the urethra and the suprapubic tube still in the bladder. Three weeks following operation the urethral tube was removed and the bladder distended with water through the suprapubic tube. The child at once voided a large stream through the urethra and seemed to have fair control. Six months later he voided well through the urethra.

SUMMARY

The literature on transposition of the penis and scrotum has been reviewed. An additional case with plastic reconstruction has been reported.

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PHYSIOLOGY OF TESTIS

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There has been little progress in the physiology of the testis or the prostate in the last few years. Active interest in cellular chemistry and cellular content of the testis has provided some new concepts.

We have accepted for long that the major hormonal role of the testis was the production of testosterone, presumably by the interstitial cells. However, we have known also that estrogens could be extracted from testes of the bull and the stallion. Quite recently Goldzieher has shown that significant amounts of estradiol can be extracted from human testes.

Maddock and Nelson have shown that an increase in urinary estrogen occurs following treatment of men with chorionic gonadotrophin and conclude that this increase is related to the increased activity of the Leydig cells.

Doctors Huggins and Scott and others feel that the Sertoli cell is the source of origin of testicular estrogens. This is certainly true in the dog which can develop a Sertoli cell adenoma. The localization of estrogen production is less certain in man, there being no very precise cytochemical method of identifying this steroid.

We have made some effort to identify and localize specific substances in the human testis, but really definitive statements cannot yet be made.

The presence of lipid is shown to vary in the Sertoli cells according to age and testis pathology. The lipid of the Sertoli cells is seen as small, discrete granules in normal young men, while in young men with progressive tubular fibrosis, in cases with no germinal epithelium, the droplets are large in size, displacing the nucleus. We consider that this lipid is degenerative in nature.

It is seen that in most normal testes there is a close correlation of the amount of cholesterol and of lipid in the interstitial cells. In many normal testes of young men we have been unable to demonstrate more than traces of cholesterol. We assume that this may be due to a continuous and rapid conversion of this precursor cholesterol to an effective steroid. This assumption is supported by chemical studies on the adrenal cortex and the corpus luteum of experimental animals which demonstrate a high rate of conversion from cholesterol to the effective steroid with little storage.

We have been unable to demonstrate cholesterol in the cells of the tubule, especially the Sertoli cell which does show intense reaction for lipid.

The difference in lipid reaction in the Sertoli cells of young men as contrasted with aging individuals is striking. However, the large globular fat inclusions of the Sertoli cell appear to indicate degenerative changes, and not storage of any hormone complex.

As another method of trying to untangle the metabolic relations of the testis with especial reference to spermatogenesis has been the use of the McManus technique for mucopolysaccharides.

Read at annual meeting, American Association of Genito-Urinary Surgeons, Shawnee-on-Delaware, Pa. May 26–28, 1954.

This sugar complex is found in the normal testis of young men in the spermatozonia and the Sertoli cell in great abundance. In a 25 year old patient with sterility with tubular fibrosis there is a marked reduction of these substances, as it also is in cases with a "reduced rate of spermatogenesis." We can only deduce that this represents a metabolic defect depending on cytological, vascular or hormonal disturbances related to infertility.

The rate of testosterone production by the testis has now been given a credible figure. We have known that a typical young male eunuchoid could be maintained on a daily dose of 25 mg. o.d. of testosterone propionate with maintenance of a positive nitrogen balance and reduction in creatinine excretion, but have had little information of the physiological rate of production of this steroid.

By two ingenious human experiments, Dobriner, Gallagher, et al. at the Sloan-Kettering Institute have shown the difference in the excretion rates of androsterone and etiocholanolone in normal human males. Preparations of testosterone were labeled either with C^{14} or deuterium. These labeled steroids were put in a microcrystalline suspension, which was then put into a solution of human serum albumin and saline. The solution was administered by intravenous infusion continuous over an eight hour period in normal men.

By computing the excretion patterns of etiocholanolone and androsterone, the two principal conversion metabolites of testosterone, during the first 48 hours after injection, the total amount of recovery could be determined. There was close agreement between this method and recovery of labeled substances.

From these very accurate and important studies these investigators state, and I quote, "It was calculated that the daily production of testosterone by a normal man does not exceed 36 mg. and that less than 17 mg. per 24 hours is a more credible estimate."

As you know the recovery of steroidal estrogens excreted in the urine after injection is very low—about 7 to 10 per cent of hydrolyzed or conjugated estrogens may be recovered in the urine, the major pathway of excretion being by way of the entero-hepatic system with biliary excretion of most estrogens in the feces.

In contrast to this Dobriner, Gallagher et al. have reported that only about 5 per cent of the labeled testosterone could be recovered in the feces and little or none of the usual degradation products.

This points up a significant difference in the metabolic pathways of gonadal steroids between men and women, and affords essential background material when one speculates on the cancerogenic role of estrogens and androgens in woman and man.

SUMMARY

In closing it might be said that the pressing needs for further research on testis physiology relate to the pituitary gonadal action and the role of steroids in spermatogenesis. There is still no direct knowledge of these problems as related to the human testis. As a result of our meager information we are almost helpless in starting the metabolic machinery by which deficient testes may be induced to make sperm, or make adequate amounts of spermatozoa for complete fertility.

I am sure that the materials are in our hands but we have been totally unsuccessful in applying them. In the case of the pituitary gonadotrophins the available preparations which are proteins in nature are currently both too impure and of a low potency. Of the available steroids we have not yet been able *consistently* to achieve our goal. The basic groundwork of research has not yet been finished and we are left rather impotent in any therapeutic methods for relief of male infertility.

The opportunity afforded for studies in steroid metabolism by the newer attempts at a palliative therapy of inoperable or recurrent breast cancer has advanced our understanding of these processes to a marked degree. Very extensive group efforts have been made to find some steroid complex which might be cancerostatic and an effective pituitary inhibitor, without the undesirable virilizing effects of the androgens. To date such cancerostatic activities of these preparations are directly correlated with their virilizing effects.

The search for new compounds which might properly and effectively regulate and control the activity of the anterior pituitary will continue. Within this framework of metabolic interaction between the trophic hormones of the pituitary and the steroid production of the adrenal, testis, and ovary, lies the answer to many metabolic diseases, and the solution may, possibly, give us new insights into cancer itself.

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CLASSIFICATION OF TUMORS OF TESTIS: A CLINICAL AND PATHOLOGICAL STUDY BASED ON 105 PRIMARY AND 13 SECONDARY CASES IN ADULTS, AND 3 PRIMARY AND 4 SECONDARY CASES IN CHILDREN

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An interesting family of tumors is that which originates in the testis (Dean; Dixon; Friedman and Moore; Rusche; Sauer, Watson and Burke; Scully). The family divides itself into 2 main branches; one branch that usually yields to surgery and/or radiotherapy and another that is more aggressive and frequently resists any form of therapy. This difference in response is striking in pure strains of the two divisions, but there are mixed and hybrid forms in which the pathological patterns are complex, the clinical course is variable and the outcome unpredictable. It is important therefore to have a comprehensive classification of all testicular tumors. Many classifications have been made but some are complicated and confusing and others incomplete. I should like to submit a "working" classification of this disease (fig. 1, table 1). The classification is based on the following postulates:

1. That the majority of tumors of the testis arise from its component elements. The significant cells that comprise the latter are:

a) Spermatogones and their derivatives. These are the "germ" cells and tumors that originate from them are "*germinal tumors.*"

b) Interstitial cells, Sertoli cells and cells that line the rete testis. Tumors arising from these cells and from the testicular stroma are the "*nongerminal tumors*".

2. That the family of "germinal" tumors is composed of two subgroups because of differences in response of the original germ cells to some unknown carcinogenic agent(s) or factor(s). The response varies as follows:—

a) When the germ cells are stimulated to divide and multiply but at the same time *retain* their trigerminal potential and maintain the original appearance, the resultant tumor is a unicellular mass known as seminoma.

b) When the carcinogenic agent(s) or factor(s) not only stimulate the cells to divide but at the same time also force them to *release* the trigerminal potential inherent in their nuclei (this without benefit of union with an oöcyte), then a chain of events is set in motion which simulates the development of an embryo (fig. 1). The resultant masses comprise the embryomatous and teratomatous tumors. In normal pregnancy the fertilized ovum rapidly divides to form a blastula with an inner cell mass and an outer ring. Chorionic cells differentiate from the latter. The counterpart for this stage is seen in the embryomatous tumors.

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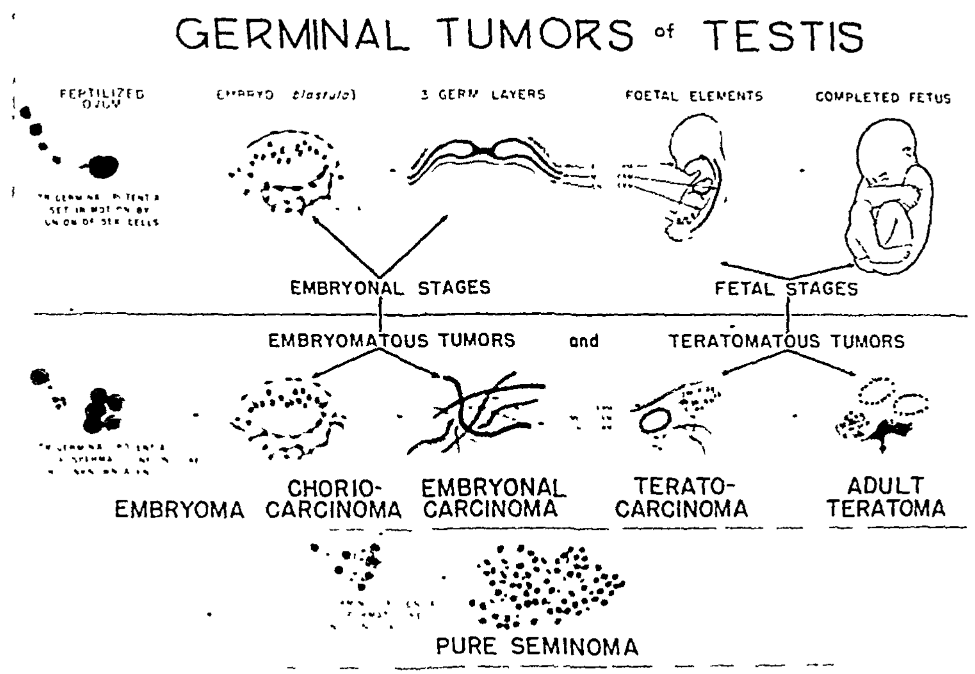


FIG. 1

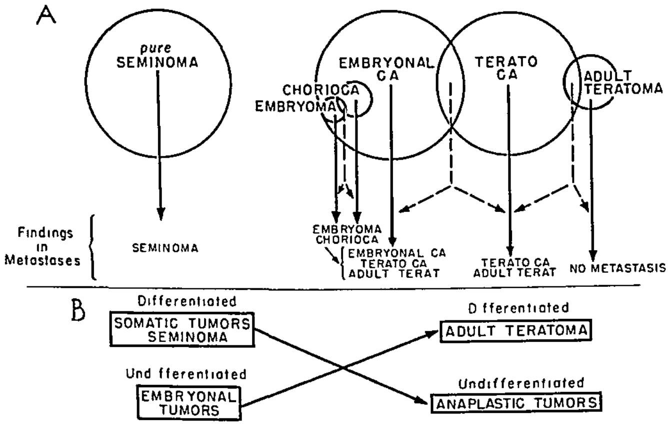
On rare occasions one does encounter a tumor that contains blastulas (embryoma) accompanied by chorionic tissue (choriocarcinoma). In normal pregnancy the blastula quickly breaks into a well recognized pattern of three germ layers: ectoderm, mesoderm and endoderm. The blastulas in the testis, too, are transformed into such layers. The compression by neighboring tissue and the 'unnatural' environment produce a hodge-podge distortion of the primary layers, with some layer, usually endoderm, outgrowing the rest (*embryonal carcinoma*). In normal pregnancy the three germ layers now tend to differentiate into tissues, organs and systems. Should an aberration occur at this stage then a teratoid monster may form. On the basis of the postulate one surmises that similar attempts at differentiation into tissue elements within the distorted primitive layers of a germinal tumor result in the formation of a *teratocarcinoma*. Complete differentiation into organs and systems characterizes the normal fetus at term. In an *adult teratoma* of the testis there is likewise an advanced differentiation of the conglomerate mass into tissue and organoid elements (fig. 1).

It is to be expected that the extremes in these groups of germinal tumors would be rare, and they are indeed: embryomas, because they are temporary and unstable and quickly go to form embryonal carcinomas; and adult teratomas, because in most cases metastases, in either the embryonal or teratocarcinoma stages, kill the patient before local differentiation can occur. Choriocarcinomas, too, are infrequent. They are highly invasive, can cause local hemorrhage, infarction and scarring and thus they may leave no local trace in the testis (fig. 2, *A*). Their metastases, however, can grow luxuriantly and destroy the host. Embryonal carcinomas and teratocarcinomas constitute the major portion of germinal testicular tumors.

TABLE 1 *Classification of tumors of testis*

Primary
- I Germinal
  - 1) Pure seminoma
  - 2) Embryomatous and teratomatous tumors
    - Embryomatous
      - a) Embryoma
      - b) Choriocarcinoma
      - c) Embryonal carcinoma
    - Teratomatous
      - a) Teratocarcinoma
      - b) *Adult teratoma*
  - 3) Combinations of 1 and 2, and of the subgroups of 2
- II Nongerminal
  - 1) Interstitial cell tumors
  - 2) Sertoli cell tumors
  - 3) Tumors of rete testis
  - 4) Miscellaneous Tumors—?androblastoma, ?gynadroblastoma, ?granulosa cell tumor, unclassifiable tumors
  - 5) Tumors of testicular stroma—fibroma, lipoma, hemangioma, etc

Secondary
- I Lymphomas, plasmacytomas, leukemic and lymphocytic infiltrations, etc
- II Carcinomatosis with involvement of testis



F[illegible] tumors Seminoma and embryonal tumor ma[illegible] contain one or both components Over lapp[illegible] circles Chorionic elements in embryoma ma[illegible] asion and infarction Distant chorionic metastasis can thrive while locally only scar remains and/or embryonal elements may differentiate through into teratocarcinoma or adult teratoma

B, behavior pattern of cell components of testicular tumors Histologically, seminoma behaves like other somatic tumors while embryonal testicular tumors simulate processes in embryo Former are differentiated at start and tend to become anaplastic, latter start as anaplastic cells and tend to become differentiated

B. *Secondary* 4 cases

to the lymphomas	2 cases
to sympathicoblastoma	1 case
to retinoblastoma	1 case

SEMINOMA

Seminoma, the "somatic" tumor of the testis, is usually a painless, smooth, hard, heavy mass, homogeneous in consistency and pinkish on section. Greyish areas of necrosis, sometimes resembling caseation, are often present, and occasionally small foci of fresh hemorrhage. The microscopic sections reveal masses of fairly large, usually oval cells with prominent, well staining nuclei. It is for this reason that the tumor has been called unicellular, monocellular or large cell carcinoma. Branching connective tissue trabeculae divide the masses of cells into compartments. A lymphoid stroma of variable intensity, said to be of good prognostic import when prominent (Dixon; Sauer, Watson and Burke), is seen in the stroma (fig. 3). The neighboring testicular tissue is compressed, the tubules are usually atrophic and interstitial cells are variable. Occasionally their lining cells show enlarged hyperchromatic nuclei which resemble those of seminoma. They may be actual tumor cells that have infiltrated the lumen or may represent an *in situ* change of spermatogones, stimulated to activity by "contagion of malignancy". It has been noted that a real increase in interstitial cells is usually associated with a less favorable outcome than when their number is unchanged or diminished (Dixon). Anaplasia is accompanied by variation in cell and nuclear size and shape, an increase in mitoses, and a decrease in stromal elements and lymphocytes. Seminomas tend to metastasize via lymphatics, and usually land in the retroperitoneal lymph glands and lungs, but metastases to other areas or organs are not uncommon. Seminomas are usually highly radiosensitive.

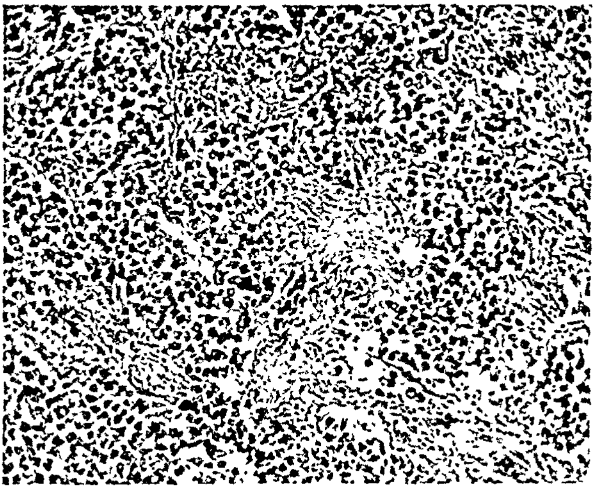


FIG. 3. Seminoma pattern. Note masses of large cells, connective tissue trabeculae and lymphocytes. Latter were perceptibly diminished in fatal cases.

A diagnosis of seminoma was made in 55 patients either by examination of the *excised* scrotal mass (51 times), abdominal mass (P. C.) (1 time), retrovesical mass (P. L.) (1 time), or on *biopsy* of the abdominal mass (L. S.) (1 time), axillary lymph node (B. Z.) (1 time). One patient (T. W.) had a positive Virchow node and another (A. H. S.) had positive right inguinal and femoral lymph nodes. All tumors in this group, except 2, were pure seminomas. The mixed seminomas contained a solitary focus of adult teratomatous tissue: cartilage in one and sebaceous cysts in the other (Mason). Both patients are alive and free of tumor more than 5 years following orchiectomy. Seminoma *components* and cells resembling 'seminoma' cells were seen in 3 patients with embryonal carcinoma and in 2 patients with teratocarcinoma. These findings are included in the latter subgroups.

Symptoms and their duration. The usual complaint was painless swelling in the scrotum. Occasionally the patient noted a dragging sensation and rarely he complained of backache. Frequently the tumor was discovered accidentally while bathing, or during some activity such as wrestling or bicycle riding. In one patient (P. R.) the tumor was discovered during a routine physical examination. One patient's (T. W.) chief complaint was a swelling in the neck and neither he nor his physician was aware of the tiny mass involving his right testis. After receiving the pathological report of seminoma on the biopsied cervical lymph node the finding prompted a more careful examination of the scrotal contents.

Many patients gave a history of mild or moderate trauma; usually, however, this was an *a posteriori* thought. Severe trauma, such as a direct kick to the testis, or being struck locally by some other solid object, was a serious complication and was usually followed by metastasis and death. The scrotal mass in four of the patients was tapped several times because hydrocele was suspected. Hydrocele fluid was found in association with tumor in only one of these cases (J. W.). In the remainder, however, dry or bloody taps had been obtained. Two of these patients died of metastases. In the fourth (P. R.) excruciating pain and marked swelling of the scrotum developed after the tapping. An emergency operation was performed for what was thought to be a hematoma but a large seminoma with areas of hemorrhage was found. The patient is alive and free of tumor 18 years after orchiectomy. These experiences suggest that tapping a tumor of the testis is equivalent to any other severe trauma and this in addition to the delay in instituting adequate treatment may help to disseminate the disease.

Out of 36 patients who survived for 2 years or more, in four the duration of symptoms before operation was unknown. In 2 patients (J. S.; J. W.) with tumor and hydrocele, symptoms had been present for 1½ and 3½ years. In one case (N. S.) with a previous orchiopexy, the swelling had been present for 2 years. In the remaining 28 patients the average duration was 5.6 months. In 13 patients who died, the duration of symptoms before operation was considerably longer in the majority of the cases. In seven it was 15 months and in 3 patients the swelling had been present for 3, 5 and 8 years respectively. Two patients (S. R.; A. S.), however, came for relief only 2 and 3 months after discovering the mass but nevertheless succumbed to the disease.

Age. The age incidence for seminoma showed a peak in the 30–40 year group (fig. 4), more than half of the tumors having occurred during that decade. The youngest was 21 years; the oldest 74 years. Two out of 7 patients in 20–29 group

The sources of some of the gonadotrophins and their effects are not completely known or understood. The pituitary gland does elaborate a follicle stimulating (F.S.H.) and leutinizing hormone (L.H.). The former produces hypertrophy of the uterus and an increase in weight of the ovaries of an injected immature rat. The latter causes hyperemia, ovulation, corpora hemorrhagica and corpora lutea. In the rat the presence of hyperemia is considered a positive reaction (positive Aschheim-Zondek test). During pregnancy chorionic tissue elaborates a powerful gonadotrophic hormone which is excreted in the urine and which can induce changes similar to the leutinizing hormone. Choriocarcinoma also elaborates gonadotrophins and the urine of a patient with such a tumor causes changes in an injected animal similar to those seen in pregnancy.

It has, however, been noted that follicle stimulating hormones, anterior pituitary-like hormones, may be present in the urine under a variety of circumstances (Engle; Gold; Melicow, Robinson, Ivers and Rainsford). This, plus the *personal equation* involved in interpreting the findings in the ovaries and uterus of an injected rat, has resulted in false reports. One of the conditions that may stimulate the pituitary to excrete gonadotrophic hormones, is unilateral or bilateral orchiectomy. The reduction or cessation of the inhibitory effect by testosterone may be the factor. Thus the Aschheim-Zondek test should be performed both *before* and after orchiectomy so as to avoid the possible confusion which may follow a positive postoperative report without a preoperative one for comparison.

Gynecomastia, too, can occur under a variety of conditions. The common denominator in all apparently is estrogenic excess. The latter may come from any of many sources (Berthong, Goodwin and Scott; Engle; Gold; Melicow, Robinson, Ivers and Rainsford; Selye, McEven and Collip). Even seminoma is said to occur with gynecomastia and/or a positive Aschheim-Zondek test. Since microscopic sections of an embryonal carcinoma may superficially resemble a seminoma and since block sections of a testicular tumor are usually not prepared, some doubt is thrown on the accuracy of the diagnosis of seminoma in these cases. The destruction or removal of androgenic elements (by unilateral or bilateral orchiectomy or disease) may allow the unopposed accumulation of estrogens, from other sources (?adrenal cortex), which is then reflected in development of gynecomastia.

In several patients in our series gynecomastia developed after unilateral orchiectomy for tumor. Their urine gave negative Aschheim-Zondek reactions before operation. It is of interest to note that 2 patients (J. W.; L. R.), age 33 and 71, came primarily for relief of gynecomastia. Biopsies of their breasts showed hyperplasia. One of the patients had had an orchiectomy for undescended testis and the other for tumor 25 years prior to the present illness and in each a neoplasm was found in the remaining testis. It was suspected before operation that they had embryonal carcinomas with trophoblastic elements, but such was not the case. Only seminomas were found. The positive Aschheim-Zondek test may have been due to an excess of gonadotrophins elaborated by overactivity of the pituitary gland uninhibited because of destruction of the remaining testis by tumor.

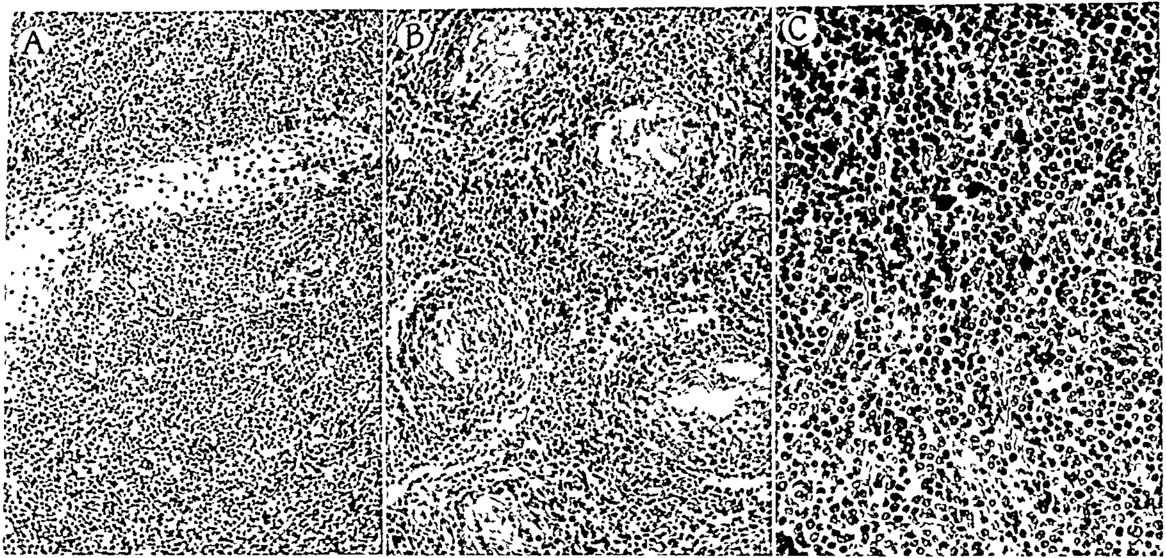


FIG. 5. Secondary tumors of testis. *A*, lymphosarcoma. *B*, plasmacytoma. Note tumor cells surrounding tubules. *C*, high power of plasmacytoma

TABLE 4. *Operations on 100 cases of germinal tumors of testis*

	Total Number of Cases	Excluded from Survival Rate Table			Available for Survival Rate Table		
		Orchiectomy elsewhere	Biopsy only	D. of other cause	Orchiectomy at Squier Cl.		
					Simple	Radical	Abdominal
Seminoma	55	2	2*	2†	33	14	2*
Embryonal carcinoma	23	1	1	—	14	7	—
Teratocarcinoma	17	1‡	—	—	14	2	—
Adult teratoma	5	—	—	—	3	2	—
Total	100	4	3	2	64	25	2

* There were 3 patients with cryptorchid testes: 2 in lower flanks (1 excision, 1 biopsy); 1 retrovesical excision (i.e., tumor in ectopic testis).

† One patient was killed 1 yr. after orchiectomy, 1 died of pulmonary embolus 2 days *p.o.*

‡ This was a radical operation performed at Fort Tilton Hospital.

Seminoma versus lymphosarcoma. There were 4 patients, ages 54, 56, 60 and 67, in whom an erroneous diagnosis of seminoma was made either on the biopsy (1 time), operative specimen (2 times) or at autopsy (1 time). All suffered from lymphomatous tumors. An anaplastic seminoma and a bizarre lymphoma may be confused for one another, particularly when the *presenting* symptom is a scrotal mass. It is important to call attention to this possible error since the prognosis in the two diseases is so different, being fairly good in seminoma and ultimately hopeless in lymphosarcoma. The age incidence is about the same. Lymphosarcoma may involve scattered lymph gland groups whereas seminoma usually involves regional portals first. Cutaneous nodules are not unusual in lymphosarcoma but such a manifestation of metastasis from a seminoma was not encountered in our series.

Seminoma and other primary tumors of the testis usually expand and compress neighboring testicular tissue and thus a sharp line of demarcation tends to form which separates the two. In secondary tumors, particularly the lymphomas, the neoplastic cells flow like lava between tubules disrupting and distorting them (fig. 5). The atrophic tubules appear as islands in a sea of neoplastic cells.

Operative procedures. Simple orchiectomy through a scrotal or inguinal incision was performed 35 times; the radical operation which included a dissection of the retroperitoneal fascia and lymph nodes, limited usually to the same side as the tumor, 14 times; and abdominal resection for tumor in undescended and ectopic testes, 2 times (table 4). The survival rate is listed in table 2.

THE EMBRYOMATOUS TUMORS

Embryonal carcinoma includes embryoma, choriocarcinoma and a group of tumors of varied microscopic pattern. All these neoplasms are uniformly aggressive and almost all display a predilection for vascular invasion. Some of the patients complained of a painful scrotal swelling which was irregularly hard and at times tender. On section the tumors appeared as pinkish masses lined with jagged, grayish, moth-eaten borders. They frequently contained scattered crimson pools of fresh hemorrhage.

The type of embryonal tissue that developed following the release of the trigerminal potential was probably governed by general and local, biological, chemical (?endocrine), physical and other unknown factors. The latter probably varied in every case. It was not surprising, therefore, to have found few embryonal carcinomas that had an identical microscopic layout. *Variation* was the essential characteristic of this tumor. The sections on rare occasion showed blastula-like structures (embryoma), lying in a wild stroma containing foci of chorionic tissue and hemorrhage (figs. 6–8). Usually the hodge-podge of embryonal tissue showed a preponderance of tissue elements which were interpreted as of endodermal origin. Papillary formations and pseudoglandular structures were present (embryonal adenocarcinoma). Intertwining infolded layers of fairly large cells supported by a vague mesenchymal stroma were frequently seen. At times the tumors were made up of small cells in clusters surrounding small spaces. This pattern has been labeled mesodermal carcinoma. Tumors with myxomatous components also occurred. There were three typical embryonal tumors associated with masses of large cells that closely resembled seminoma. Finding seminoma cells near an embryomatous tumor was not surprising since not all germ cells need necessarily have released their trigerminal potential in response to the carcinogenic agent(s) or factor(s). There were several embryonal carcinomas whose cell pattern superficially resembled seminoma (fig. 8, *B*), but close examination revealed a solid array of large cells almost devoid of connective tissue trabeculae and lymphocytes. Block sections eventually exposed foci of papillary and pseudoglandule formation. A few of the tumors showed a sprinkling of tissue that had undergone slight differentiation along the lines of a teratocarcinoma. The merging of embryonal carcinoma with teratocarcinoma can be explained on the basis of the moving picture process as expressed in the postulate. The line of demarcation between embryonal carcinoma and neighboring testicular tissue was not a sharp one. Infiltration between tubules and into the lumen of tubules was seen often. Masses of large, elongated, deep staining cells in syncytium were characteristic of chorionic tissue (Atkinson; Ogden), but occasionally solitary, hyperchromatic, giant cells were also present. Signet ring, smudgy, curvaceous cells lying in close proximity to paler cells, which have been called appliqué cells, were also encountered. They are looked upon by many as a form of chorionic cell (fig. 7, *C*).

There were 23 patients, in our series, on whom a diagnosis of embryonal carcinoma was made. In one, only a biopsy was possible, and in another orchiectomy had been performed elsewhere. In the remaining 21 patients, simple orchiectomy was performed 14 times and the radical operation 7 times (Cahill). Of the former one had his operation 1 year ago and is alive and free of cancer to date and four are alive more than 5 years since their operation. In eight out of nine patients who died of their disease, the average duration after the simple orchiectomy was 8 months, the shortest was 2½ months and the longest 17 months. In one patient the exact date of death is unknown. Of the 7 patients who had the radical opera-

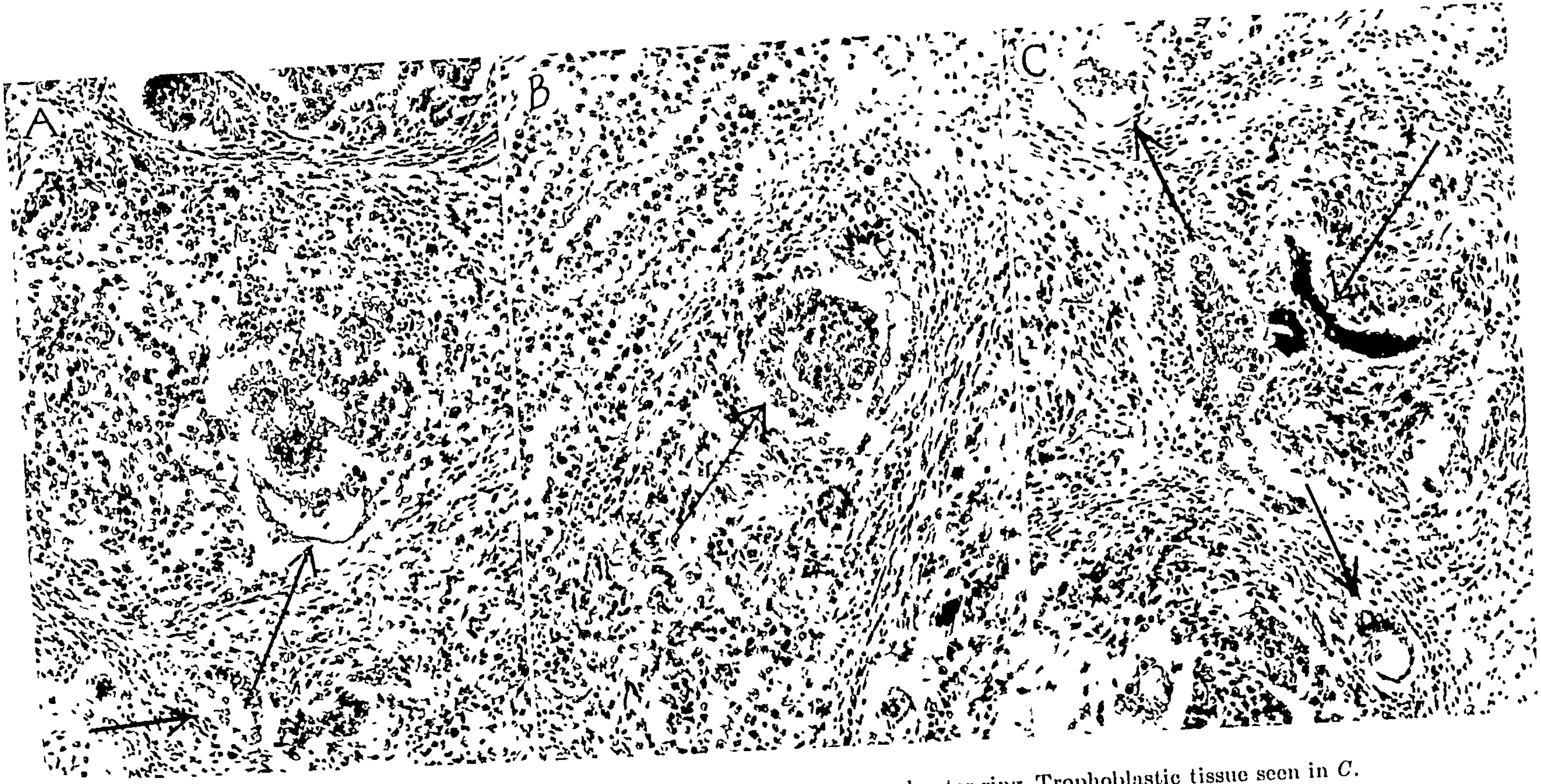


FIG. 6. Embryoma patterns. Note blastulas with inner cell mass and outer ring. Trophoblastic tissue seen in *C*.

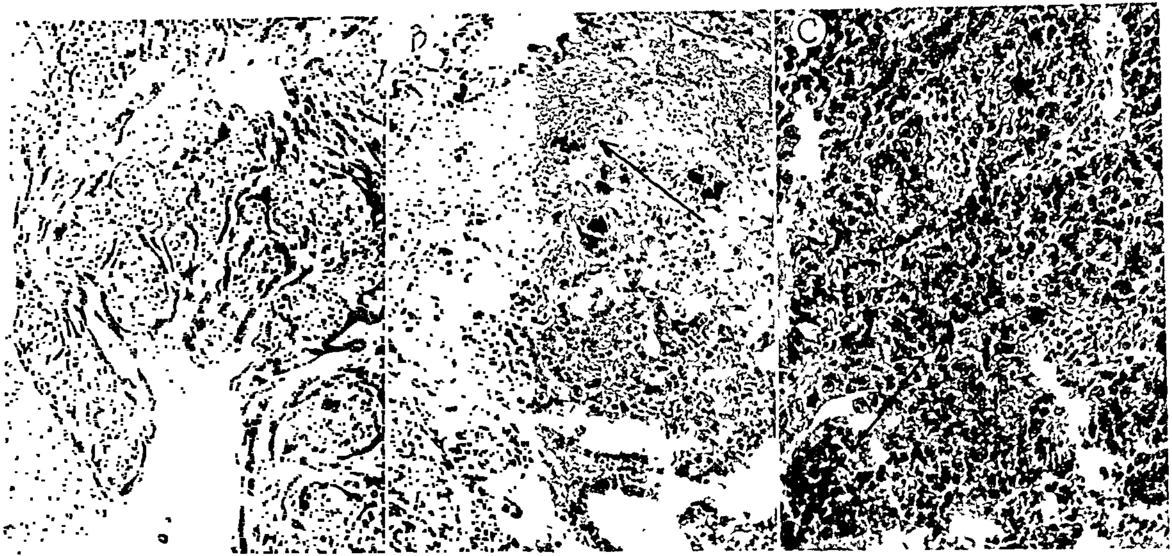


FIG. 7. Choriocarcinoma patterns. *A*, syncytiotrophoblasts and cytotrophoblasts. *B*, clusters of chorionic cells invading blood vessel. *C*, appliqué cells in embryonal carcinoma.

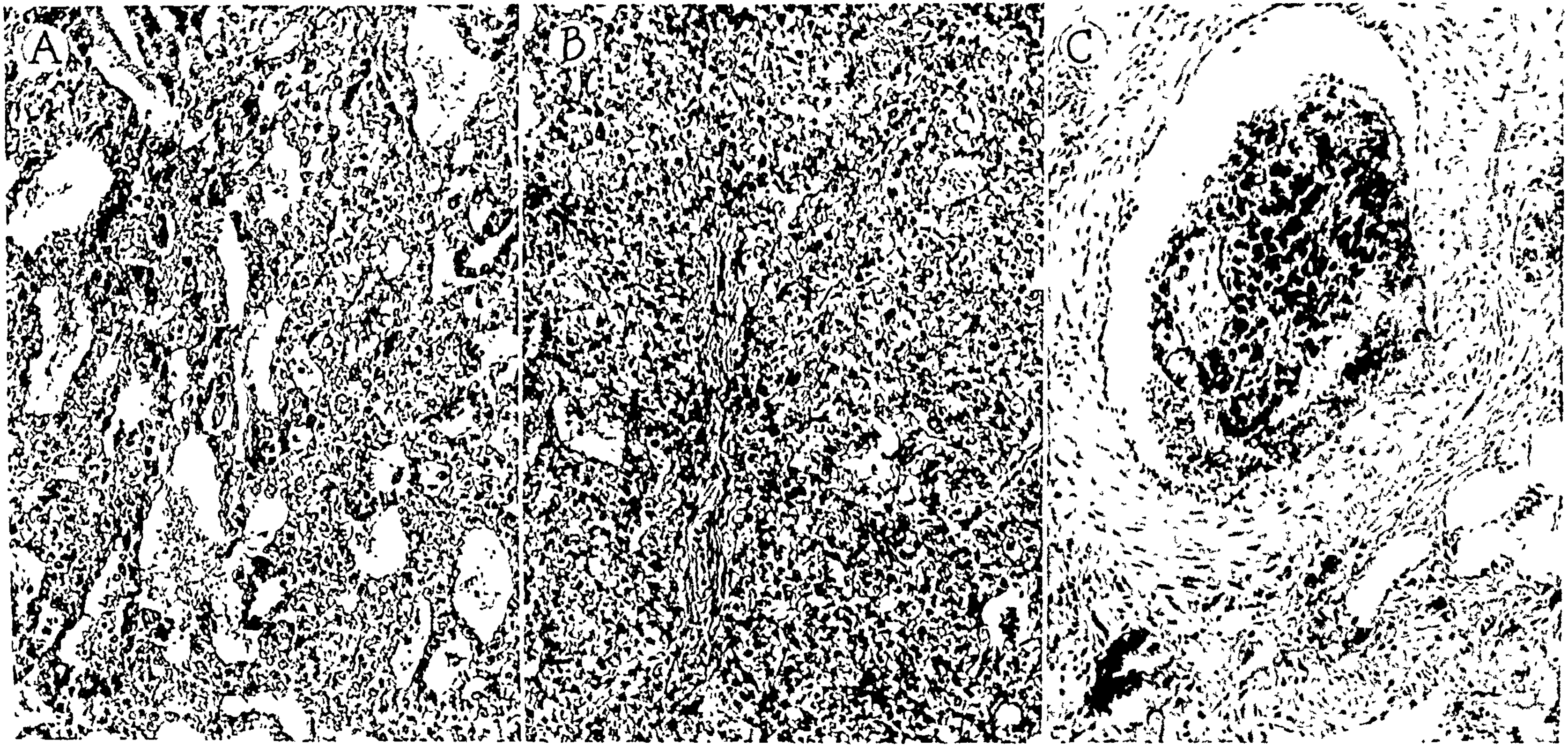


FIG. 8. Embryonal carcinoma. *A*, glandular pattern. *B*, solid cell pattern. *C*, invasion of blood vessel.

tion, four survived 1, 5, 5½ and 12 years respectively; and the duration after orchiectomy of the three who died was 14 days, 6 and 7 months. The radical operation in this small series of cases seemed to offer greater hope of salvage. The study also indicated that patients surviving 2 years without recurrence may have escaped the disease (table 2).

Symptoms and their duration. The usual complaint was a unilateral swelling of the scrotum accompanied, in about half the cases, by local pain and/or tenderness. Two patients complained of backache, one of pain in the chest, one of hemoptysis and several of loss of weight and weakness. Severe trauma seemed to play an important role in spreading the disease in 6 cases. One patient (J. C.) gave a history of injury to his left testis when he fell off a scaffold. This occurred 10 months prior to admission to the hospital. Another patient (N. G.) stated that his left testis was hit by a pitched ball 4 years before his present illness. The testis had remained large ever since the accident but suddenly increased in size over a period of 3 months. A third patient (A. B.) was kicked in the left testis 2 months prior to his admission to the clinic. Three other patients also gave a history of severe blows to their testes one to several years prior to seeking relief for the swollen organs. All but one of these patients died of metastases.

One patient (A. B.) came to the clinic because of the discomfort caused by an abdominal mass. During the routine examination a swelling of the left testis was discovered. The excised tumor proved to be an embryonal carcinoma and the abdominal mass a metastasis. An interesting case with a multiplicity of lesions in the same testis was that of a 28 year old patient (R. D.) with a history of mumps at the age of 9. He had lived in the Belgian Congo for 15 years and while there became ill with malaria and filariasis. He then came to the Squier Clinic for relief of a markedly swollen scrotum. Aspiration of the right testis revealed adult Filaria volvulus, filariasis was also found in 5 skin biopsies and Plasmodium falciparum in the blood. The cervical lymph nodes were swollen, and numerous hard masses could be palpated in the region of the thyroid gland. Clinically it was thought that in addition to the filariasis he also had carcinoma of the thyroid gland. A biopsy obtained from the neck showed a malignancy of unknown origin and a biopsy of the testis showed a cicatrix. The patient died 4 months later and autopsy revealed an embryonal carcinoma of the right testis with generalized metastases.

The longest duration of symptoms in embryonal carcinoma, before orchiectomy, in patients who survived 5 years or more was 6 months, and in the majority it was 3 months. The average duration in 10 patients who died of this disease was 14 months but there were some cases even in this group in whom the symptoms had been present for 1 to 3 months only. There was one patient (R. O'B.) age 51, whose swelling of his right testis had been noted for only one week, yet retroperitoneal metastases were found and removed at the time of the operation. This patient has survived 2 years to date without recurrence.

Age. The age incidence in embryonal carcinoma was greatest between 20 and 35 years (13 out of 23 patients). The youngest was 19 and the oldest 61 years of age (fig. 4).

Size and weight. There seemed to be no significant relationship between size or weight of embryonal carcinoma and survival. The tumors as a group were smaller than those seen in seminoma. The lightest weighed 36 gm. and the heaviest 205 gm.

Side. Eleven of the tumors were located in the right testis and 12 in the left (table 4). In seven out of 9 patients who survived 1–17 years after orchiectomy the tumor was located in the right testis; in only 2 patients did it arise in the left testis. On the other hand, in 14 patients who died of embryonal carcinoma, the left testis was the primary site in 10 patients and the right in 4 patients. This difference may be due to the great propensity of embryonal carcinoma for vascular invasion, and the direct spread afforded by the left spermatic vessel.

Gynecomastia and the Aschheim-Zondek test. There were 4 patients with embryonal carcinoma, three of whom had gynecomastia and positive Aschheim-Zondek tests before orchiectomy and one in whom only urinary gonadotrophins were present. In all the cases typical chorionic tissue was found and all died of metastases.

One of the patients was a 28 year old man (N. O.) whose left testis had been struck by a pitched ball. Sections of the tumor showed an embryoma and choriocarcinoma. Numerous blastulas of varying size and shape were also found (fig. 6, *A*). The case was reported by us in detail in the *Journal of Urology* in 1940.

Another patient (W. C.), age 34, had a radical excision of an embryonal carcinoma. Only a few clumps of trophoblasts were seen but several hemorrhages and an area of infarction were also present. One year later the patient returned with symptoms of gastro-intestinal obstruction and an upper abdominal mass. Operation showed invasion of the duodenum by a retroperitoneal tumor which on biopsy revealed chorionic tissue. Two patients (B. R. 31 and C. C. 34 years) had chorionic elements in their tumors but did not show gynecomastia.

In conclusion, embryonal carcinoma is a tumor of diverse pathological pattern but of uniform potential for invasiveness, particularly via vascular channels. It runs the gamut from blastula with chorionic support to germ layer preponderance. It is a fascinating pleomorphogenic tumor.

TERATOCARCINOMA

On the basis of the postulate teratocarcinoma may be looked upon as a partially differentiated embryonal carcinoma. It usually occurred as a large, nodular, oval mass, honeycombed with cysts, interpolated with greyish, glistening, gristly areas of cartilage, or flaked with foci of hemorrhage or necrosis. The microscopic sections revealed a kaleidoscopic array of spaces lined by columnar epithelium of endodermal origin, and/or of cystic areas lined by a keratinized epithelium of ectodermal origin, and/or scattered foci of young cartilage of mesodermal origin. Nerve elements with rosette formations, goblet cells, pigmented structures and a variety of structures vaguely resembling those of distant organs have been reported. The intervening tissue was usually mesenchymal in appearance and wildly growing like that in embryonal carcinoma (fig. 9).

There were 17 cases in this subgroup. It is of interest to note that four of the

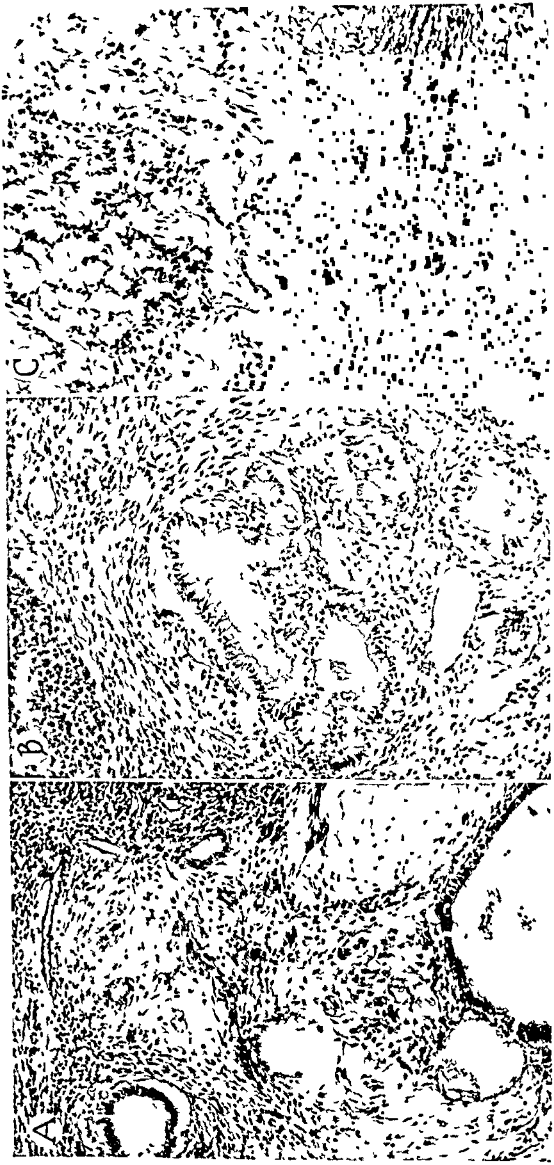


Fig. 9 Teratocarcinoma *A*, pseudoglandules in malignant stroma *B*, columnar epithelium lining glands *C*, myxomatous area

cases of teratocarcinoma were originally looked upon as embryonal carcinomas until additional sections revealed areas of partial differentiation such as pale-staining young cartilage or glandular epithelium. In one patient (P. N.), age 32, two discrete lesions were found in his left testis which had become enlarged over a period of 6 months. One was an embryonal carcinoma and the other showed areas of differentiation into a teratocarcinoma. There were 2 patients with a picture suggestive of chorionic tissue in a teratocarcinoma. One was a 17 year old boy (D. P.) who was brought to the hospital with severe pain in his chest, dyspnea, hemoptysis, loss of weight and appetite, of 2 weeks' duration. Radiographs of the chest revealed metastatic malignancy. A tiny nodule was felt in the left testis. A left hydrocele was said to have been present during infancy and had receded. The Aschheim-Zondek test was positive. An inguinal orchiectomy was performed and a small, oval cyst measuring 0.9 by 0.8 cm. was found which was lined by a keratinized squamous celled epithelium. Surrounding it was an anaplastic stroma and within the latter was the scar of an infarct. It was our opinion that a choriocarcinoma had been present which broke into a blood vessel and metastasized to the lungs but destroyed itself locally leaving an infarct and a scar. The lung metastases thrived. Locally the surviving embryonal elements went on to partially differentiate and formed a teratocarcinoma. The patient died one month after his operation. Unfortunately an autopsy was not obtainable. This case is similar to the one reported by Craver and Stewart in which autopsy proved the presence of chorionic masses in the lungs.

Teratocarcinoma is thought to be less aggressive than pure embryonal carcinomas, but invasion and metastases by the more active areas of undifferentiated tissue can and do occur. In the metastases one may find either embryonal carcinoma or teratocarcinoma. The latter probably represents partial differentiation within the metastasis.

Survival rates are shown in table 2. All deaths occurred within one year after operation. One 20 year old patient (R. C. W.), who had a radical orchiectomy, survived 5½ years before finally succumbing to metastases. He was operated on at the Fort Tilton Hospital and then received many courses of radiotherapy for metastases to the lungs. A little over 5 years later the patient was admitted to the Squier Urological Clinic with evidence of liver and lung involvement. A needle biopsy of the liver showed a metastasis from a teratocarcinoma. This postoperative duration before death was the longest in our series of testicular tumors.

In summary, teratocarcinoma is a stage between embryonal carcinoma and adult teratoma. It can therefore contain, on the one hand, elements of an embryonal carcinoma including chorionic tissue; and on the other it may show, less commonly, a preponderance of adult tissue.

ADULT TERATOMA

Adult teratoma, according to the postulate, is a germinal tumor in which complete differentiation of its embryonal elements has taken place. It is to be expected that a true adult teratoma is rare and there were only 5 cases of this

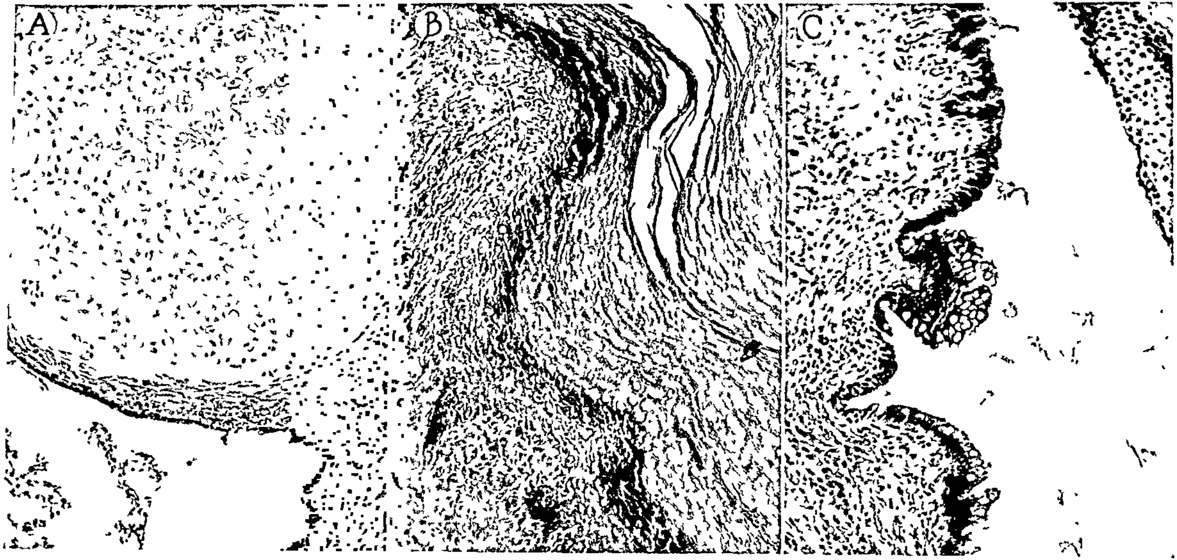


Fig 10. Adult teratoma *A*, cartilage *B*, keratinized squamous celled epithelium lining cyst space. *C*, mucin-containing cells lining glands.

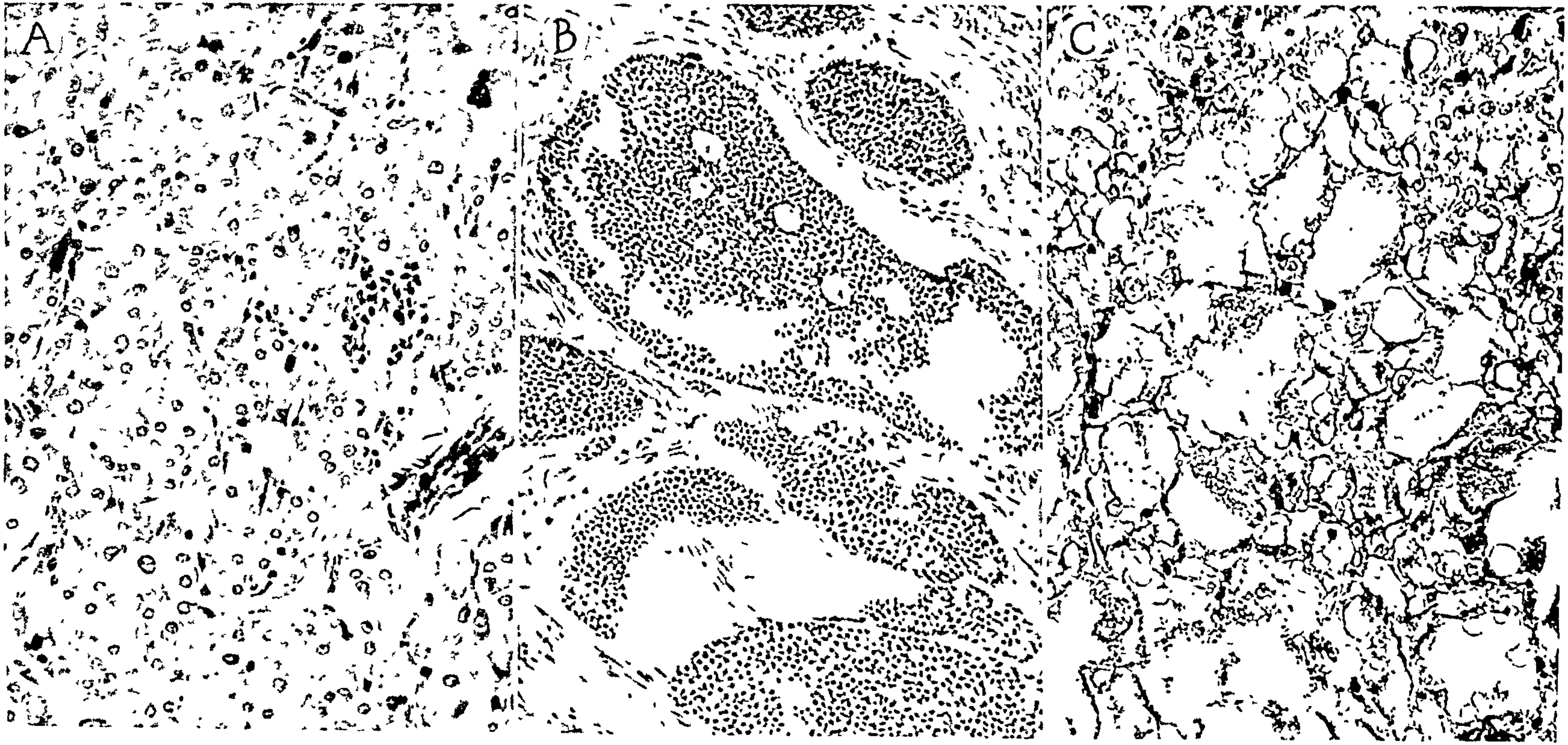


FIG. 11. *A* and *B*, nongerminal tumors. *A*, interstitial cell tumor. *B*, granulosa cell tumor. Note Call-Exner bodies. *C*, tumor in 2 year old infant.

type in our series. Two of the patients (A. G.; R. B.) were 19 years of age, one was 40 (J. B.), one was 53 (A. B.) and one was 57 (M. K.).

One tumor weighed 35 gm. and the remaining ones were large and heavy (150, 200, 300 gm.). On section they presented a varied appearance. The cut surfaces were either pinkish grey or reddish brown. Elements were usually bound closely together. Areas of fibrosis, foci of cartilage, multiple cysts containing gelatinous or straw colored fluid or cheesy material were scattered throughout the mass. At times the tunica formed a thick, bluish purple sac filled with old blood. In such cases it was difficult to distinguish the lesion from an old hematoma except by block section. The microscopic studies revealed areas of adult cartilage, bone, squamous cell cysts, mucus glands resembling intestinal glands, all lying in a relatively well differentiated adult stroma (fig. 10). Four of the patients have survived from 5 to 13 years after operation. The fifth patient (A. B.) was operated on 3 months ago at which time he was free of metastases.

It is essential in all cases to do block sections in order to ferret out a possible hidden focus of malignant tissue. Such an area would explain the incongruity of a diagnosis of adult teratoma which is benign, in the presence of distant metastases. Should the search prove futile, the diagnosis of adult teratoma may still hold since it is possible for the malignant area of a teratocarcinoma to have metastasized before it continued to differentiate locally into adult tissue (fig. 2, *A*).

TUMORS IN CHILDREN

Tumors of the testis are rare in children (Boehme, Bagley and Pumphrey; Gnotts; Magnes and Bryant). Seminomas apparently do not occur in that age group. This observation is in accord with the impression that atrophy is a prerequisite for the development of a seminoma (Haines and Grabstald).

There were 7 cases of tumors in children, three primary and four secondary. The 5 year old boy (W. A. J.) with an interstitial cell tumor has been included in the discussion of nongerminal tumors (fig. 11, *A*). The only germinal tumor in a child, in our series, was removed from an infant (T. C.) 2 years and 2 months of age in whom the testicular swelling was noted shortly after birth. The excised specimen showed a lesion which resembled the mesodermal type of embryonal carcinoma (fig. 11, *C*). He made an uneventful recovery following simple orchiectomy and is alive and well 13 years after operation. The third case was that of a 7 year old boy (J. G.) who came to the Babies Hospital because of swelling of his right testis of 3 months' duration. This was clinically diagnosed as a hydrocele. Simple orchiectomy was performed and the small testis within the hydrocele sac showed the picture suggestive of lymphosarcoma or possibly localized lymphoid hyperplasia. Survival to date after 8 years, without recurrence or evidence of metastasis, suggests that the latter diagnosis may have been the correct one.

The four secondary tumors were all found during autopsy examination. The children ranged in age from 3 to 4½ years. In all cases the testes had apparently become targets of metastatic spread from a fulminating malignancy. The primary lesions were lymphosarcoma, reticulum cell sarcoma, sympathicoblastoma and retinoblastoma (fig. 11).

NONGERMINAL TUMORS OF TESTIS

Interstitial cell tumors are uncommon (Bonser and Robson; Christeson and Nettleship; Garvey and Daniel; Grabstald, Haines and Morrow; Hooker, Gardner and Pfeiffer; Mayers; Melicow, Robinson, Ivers and Rainsford; Lewis '48; Twombly, Meisel and Stout). There were five in our series. Three were discovered following orchiectomy and two were found at autopsy. In the latter instance the patients, 53 and 71 years of age, were free of any discernible endocrine disturbance. The lesions were benign and covered many low power fields. Of the 3 patients who were operated on for testicular neoplasm, one occurred in a boy (fig. 11, *A*), age 5, whose case history was published in the *Journal of Urology* in 1949. The 5-year follow-up shows accelerated bone maturation as revealed by radiographs of the hands and forearms, and some slowing up of the precocious sexual development. It is important to call attention to case 6 in table 3 in that report—it should be excluded since it did not occur in a child. Rigoletti's case was unilateral (Garvey and Daniel).

The two interstitial cell tumors in adults who came to operation were not associated with any obvious endocrine disturbance. They were large and each measured 8.0 by 7.0 by 7.0 cm. Both patients are alive and well 7 and 8 years following orchiectomy.

The component cells of the tumors were of two types. Those in the boy were fairly large, polygonal in shape and contained discrete nuclei and prominent nucleoli. The cytoplasm was eosinophilic and often contained a homogeneous yellowish-brown pigment. Vacuoles were at times seen. These have been demonstrated as being due to droplets of isotropic fat. The cell type resembled somewhat that seen in tumors of the adrenal cortex associated with adrenogenitalism. The crystalloids of Reinke which are occasionally present in Leydig cells were not demonstrated in the neoplasms. The tumors in the adults often contained small cells rich in a homogeneous eosinophilic cytoplasm.

GRANULOSA CELL TUMOR

This unusual tumor was found in a 52 year old man (T. T.) who complained of swelling of the right testis for 5 years. It measured 13 cm. in diameter and weighed 850 gm. Sections revealed masses of small cells lying in a dense fibrous theca-like stroma which was at times hyalinized. The cell clusters contained areas which resembled Call-Exner bodies (fig. 11, *B*). The slides have been reviewed by other pathologists, including those interested in pathology of the gynecological tract, and all concurred in the diagnosis of granulosa cell tumor (Engle; Lattes). There was no indication on the patient's chart that an endocrine disturbance was present. There has been no follow-up of this case.

It is of interest to note a similar lesion reported by Cohen and Diamond in a 21 year old man with congenital anomalies of the urinary tract and generalized osteitis fibrosa.

MISCELLANEOUS TUMORS

Sertoli cell tumors, androblastomas and other nongerminal tumors, such as have been reported in medical literature (Lewis and Stockard; Teilum) were not encountered in our small series of nongerminal tumors. There was an incidental finding of an adrenal cortical rest in the cord of a patient (W. A.), age 35, who had a seminoma of the left testis.

SECONDARY TUMORS OF THE TESTIS

Secondary tumors of the testis were uncommon (Mason; London and Grossman; Turley and Moore) and when discovered were usually mistaken for seminoma. This was particularly true when a lymphoma spread to the gonad and the patient presented himself with a swelling of the latter as his chief complaint. It was assumed that the tumor was primary in the testis and that other masses elsewhere were metastases from it. The microscopic sections resembled a bizarre or anaplastic type of seminoma. When the chief complaint was an enlarged axillary or cervical lymph node, the condition was clinically diagnosed as lymphosarcoma, Hodgkin's disease or tuberculosis, until biopsy of a lymph gland revealed metastatic seminoma. It is important to recognize these possible errors since lymphoma is incurable at present and seminoma has a relatively good prognosis when treated adequately.

There were 13 cases with secondary tumors in our series. The age range was from 39 to 67 and the majority (Craver and Stewart) were over 50 years of age. The pathological findings ranged as follows: 1) lymphosarcoma, 4 cases; 2) reticulum cell carcinoma, 4 cases; 3) plasmacytoma, 4 cases; 4) carcinoma of bile ducts, 1 case.

Four patients had secondary lymphosarcomas of the testis. In one the condition was diagnosed correctly after orchiectomy, in another the testicular swelling was mistaken for seminoma and in the remaining 2 patients the lesions were found at autopsy. There were 4 patients with reticulum cell sarcoma. The lesions in 3 of the cases were diagnosed as "anaplastic" seminomas until a thorough review of the original and additional sections revealed the true lesion. The fourth case was clinically diagnosed as seminoma but the microscopic sections showed the picture of a reticulum cell sarcoma.

A report of the findings on the 4 patients with plasmacytoma was published in the *Journal of Urology* in January 1954.

It is important to emphasize again that primary neoplasms of the testis, particularly seminomas, tend to expand and thereby compress neighboring testicular tissue. In secondary tumors, particularly the lymphomas or plasmacytomas, the tumors tend to infiltrate between tubules with the latter lying like islands in a sea of small anaplastic cells (fig. 5).

SUMMARY AND CONCLUSIONS

A review of 108 primary and 17 secondary tumors of the testis in adults and children has been presented.

Neoplasms involved the right testis more often than the left (about 5 to 4).

Primary testicular growths were divided into germinal and nongerminal:—

a) those that developed from spermatogones (germ cells) were germinal (over 95 per cent of the total).
b) those that developed from Sertoli, interstitial and rete cells, or stroma were nongerminal (less than 5 per cent of the total.)

A classification of germinal tumors based on the following postulates was presented:—

a) seminoma is a tumor composed of spermatogones which have *retained* their intranuclear trigerminal potential.
b) embryonal carcinoma, teratocarcinoma and adult teratoma are a family of tumors derived from spermatogones from which the intranuclear trigerminal potential has been *released.*

Mixed germinal tumors were not uncommon. The postulates helped to explain the occasional discrepancy between the appearance of a primary tumor and its metastasis.

Pure seminoma tended to develop in atrophic testes. The greatest incidence was between 30–40 years; there were no patients under 20 years of age in the 55 cases of seminoma.

Seminoma usually metastasized by way of the lymphatics and tended to be radiosensitive.

In 3 patients seminomas developed in abdominal testes; one of these was in an ectopic testis.

In 2 patients seminoma developed 22 years after orchiopexy which had been performed at the ages 14 and 15, respectively. We recommend that orchiopexy be performed before puberty, between the ages of 5 and 7. Biopsy should precede the procedure, orchiectomy being indicated if atrophy is found.

The 2- and 5-year survival rates in seminoma, even in patients with preoperative metastases, were relatively good (70–80 per cent) with simple or radical orchiectomy followed by radiotherapy.

The average postoperative duration of patients who died of seminoma was 12 months, the longest was 30 months (1 case).

The largest tumors developed in abdominal testes.

The embryomatous and teratomatous tumors occurred most frequently between the ages of 20 and 35 and there were 4 patients out of the 45 cases who were under 20. All the neoplasms in this major group, except the adult teratomas, were aggressive, tended to invade and metastasize by way of the blood vessels and were radioresistant. There was a type of solid cell embryonal carcinoma which microscopically resembled seminoma.

The 2- and 4-year survival rate in the relatively small group of cases indicated a trend toward better results with radical orchiectomy than with the simple operation. All patients received postoperative radiotherapy.

The average postoperative duration of patients who died of embryonal carcinoma or teratocarcinoma was less than 1 year. One patient, with a teratocarcinoma, survived 5½ years after radical orchiectomy but finally succumbed to liver and lung metastases in spite of intense radiotherapy.

All patients with embryomas and choriocarcinomas died of their disease It is important to distinguish between chorionic cells, giant cells and appliqué cells since, in our series of cases, the latter types were not always invasive

Teratocarcinoma was the stage intervening between embryonal carcinoma and adult teratoma and there were tumors of this variety in which the former predominated and others in which differentiated tissue dominated The undifferentiated areas, however small, were significant from the point of view of malignancy and possible spread

Adult teratomas were the completely differentiated tumors They were rare It was difficult to differentiate an old hematoma with granulation tissue, fibrosis, cholesterin deposits from an adult teratoma in which hemorrhage had occurred

A positive Aschheim-Zondek test was usually obtained in patients with tumors containing chorionic tissue A pseudopositive test (FSH) may result from a variety of causes emanating from the testis or *other* foci and should not be confused with a truly positive luteinizing reaction (LH)

The Aschheim Zondek test should be standardized and performed routinely, pre- and postoperatively on all cases

Gynecomastia is usually related to hyperestrinism from any source Chorionic tissue is a major source, but there are other factors that can allow estrogens to accumulate

The majority of nongerminal tumors were of the interstitial cell variety The granulosa cell tumor in our series was an interesting pathological finding

There were 17 secondary tumors 13 in adults and 4 in children The majority were lymphomas and cancers of a similar origin

Lymphomas metastasizing to the testis were sometimes mistaken both clinically and pathologically for seminoma, particularly when the presenting symptom was a testicular swelling A correct differential diagnosis in these lesions is important, in view of the difference in prognosis

Primary testicular tumors were rare in children There were no seminomas in this group

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PERINEAL BIOPSY COMBINED WTH RADICAL RETROPUBIC PROSTATECTOMY FOR EARLY CARCINOMA OF THE PROSTATE

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CLINTON E. STURDEVANT

There are two accepted operations for total prostatectomy: the radical perineal method first described and used by Dr. Hugh Young in 1904 and the retropubic method advocated more than forty years later by Mr. Terence Millin of London.

Advantages claimed for the perineal method are accessibility of the prostate, dependent drainage, and a high cure-rate in patients properly chosen for radical prostatectomy.

Technical difficulties sometimes encountered in radical perineal operations as well as occasional damage to the rectum with resultant recto-urethral fistula, even in the hands of the most competent operators, have served to prevent widespread acceptance of the perineal approach. Also, the frequency of loss of sphincter control with partial to complete incontinence has been discouraging. Furthermore, complete removal of the entire seminal vesicle on each side, which in every case should be done, is at times difficult or almost impossible to accomplish. This is true on occasion in the hands of even the most expert perineal surgeon.

Proponents of the retropubic approach for radical prostatectomy point out that it offers easier access to the prostate and seminal vesicles, better exposure for sure dissection and hemorrhage control, less danger of rectal injury, less difficulty in complete removal of the seminal vesicles and is followed by less urinary incontinence.

The principal objection to be said for radical retropubic prostatectomy is the fact that this approach does not lend itself to a reliable biopsy procedure, hence patients are not infrequently subjected to radical prostatectomy without proper confirmation of the presence of cancer. Furthermore, once embarked on the road of radical prostatectomy by this approach the operator is committed, and after severance of the membranous urethra the procedure must be carried through.

Soon after Millin's first visit to this country, being impressed with certain advantages of the retropubic exposure, we began to use it for very large prostates and for cancers of the prostate when they were deemed to be operable. Certain criteria for performance of radical prostatectomy have evolved. They are 1) histological confirmation of cancer by biopsy, 2) absence of evidence of local spread on rectal palpation, 3) absence of demonstrable metastases by x-ray or by elevation of serum acid phosphatase, 4) satisfactory general condition and age as to life expectancy, cardiovascular renal status, nutritional state and mental outlook.

Paramount among the criteria necessary before radical prostatectomy should be performed is the histological confirmation of the presence of cancer cells. Biopsy may be done by a needle punch through the perineum into the suspected

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Read at annual meeting, Southeastern Section of American Urological Association, Palm Beach, Fla. April 12–15, 1954 area of the prostate or by transurethral resection, being certain of obtaining the suspected tissue by digital pressure through the rectum over the hard area toward the fenestra of the resectoscope as the cut is being made. Neither the needle punch method nor the transurethral approach has been found to give satisfactory results as to accuracy in diagnosis of prostatic cancer. Colby found the needle biopsy to be no more accurate in diagnosis of prostatic cancer than the examining finger of the trained urologist. By far the most reliable method of obtaining biopsy of suspected prostatic cancer is by direct perineal exposure of the posterior and lateral lobes of the prostate and removal of the thus exposed indurated portion for microscopic study. The microscopic study may be made rapidly by frozen section in which case the total prostatectomy may be performed immediately.

According to Colby, the interpretation of frozen prostatic sections was proven later to be incorrect in 8.4 per cent of cases in study of a series of radical prostatectomy patients. A similar error rate has been noted by others in diagnosis by frozen section. Often the pathologist, uncertain, may lean to the side of malignancy and an unnecessary radical procedure may be carried out.

Due to the chance of error in the interpretation of quick frozen sections, we began to perform radical prostatectomy in two stages. The first stage consists of perineal exposure of the prostate suspected of being malignant and removal by electrocutting loop of the indurated area. The perineal wound is then closed, leaving in a Penrose drain, and the biopsy material is submitted for microscopic study. The pathologist is then able to make permanent paraffin sections and study of such sections has reduced the error in diagnosis to a minimum. When cancer is present it has become our practice to perform total prostatectomy by the retropubic route in from 3 to 5 days after the perineal biopsy was done.

In every instance the radical prostatectomy was found to be much less difficult of performance than in patients who had not previously had perineal exposure of the prostate with the co-incident dissection away of the rectum from the posterior surface of the prostate. The space already present between the prostate and rectum greatly facilitates this phase of the operation usually found to be difficult. The operative time is reduced and the entire prostate along with all of each seminal vesicle is removed with comparative ease.

TECHNIQUE

The technique for the perineal biopsy is the standard approach as originated by Hugh Young. A large loop electrode using a cutting current is employed to remove the suspected portion of the prostate. Hemostasis is obtained by fulguration; the wound is closed by interrupted sutures and a Penrose drain is left in place (figs. 1 and 2).

The technique of the retropubic radical prostatectomy is essentially as described by Millin with slight modifications. A transverse abdominal incision has seemed to give better exposure than the midline incision (fig. 3). The puboprostatic ligaments are isolated and ligated. Very little blunt dissection with the finger close to the lateral surface of the prostate is needed to open into the space previously made between the rectum and posterior lobe of the prostate. The urethra

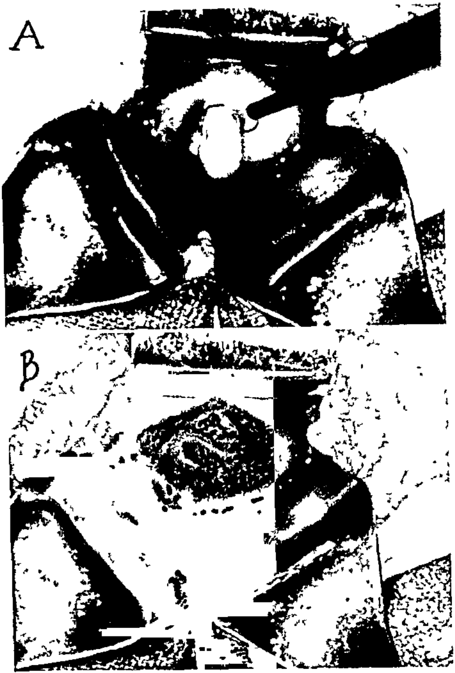

Fig. 1. *A*, showing loop removal of biopsy through open perineal exposure. *B*, posterior surface of prostate after biopsy.

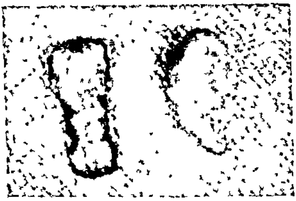

Fig. 2. Biopsy obtained by electrosurgical loop through open perineal exposure

is then divided in the membranous portion immediately proximal to the urogenital diaphragm which contains the external sphincter muscle. Further dissection of the rectum away from the prostate and bladder along with traction upward of the prostate thus divided from the urethra readily exposes the seminal vesicles. The bladder is then opened by a transverse incision in the anterior wall exposing the trigone. The floor of the bladder is incised immediately between the trigone and the prostate, care being taken not to injure the ureters The prostate is then again retracted upward and the seminal vesicles dissected free and removed, the

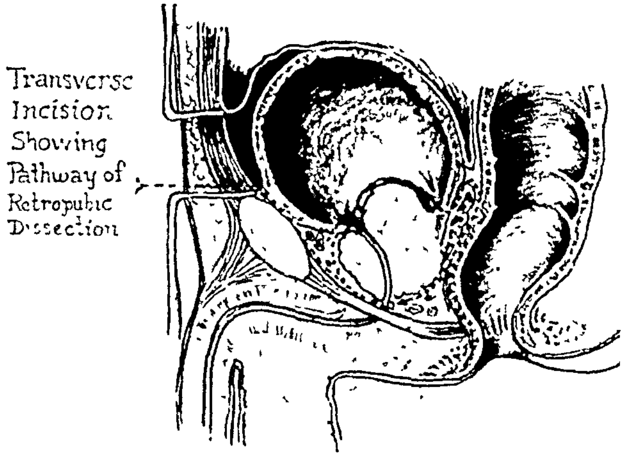

FIG. 3. Transverse incision showing pathway of retropubic dissection

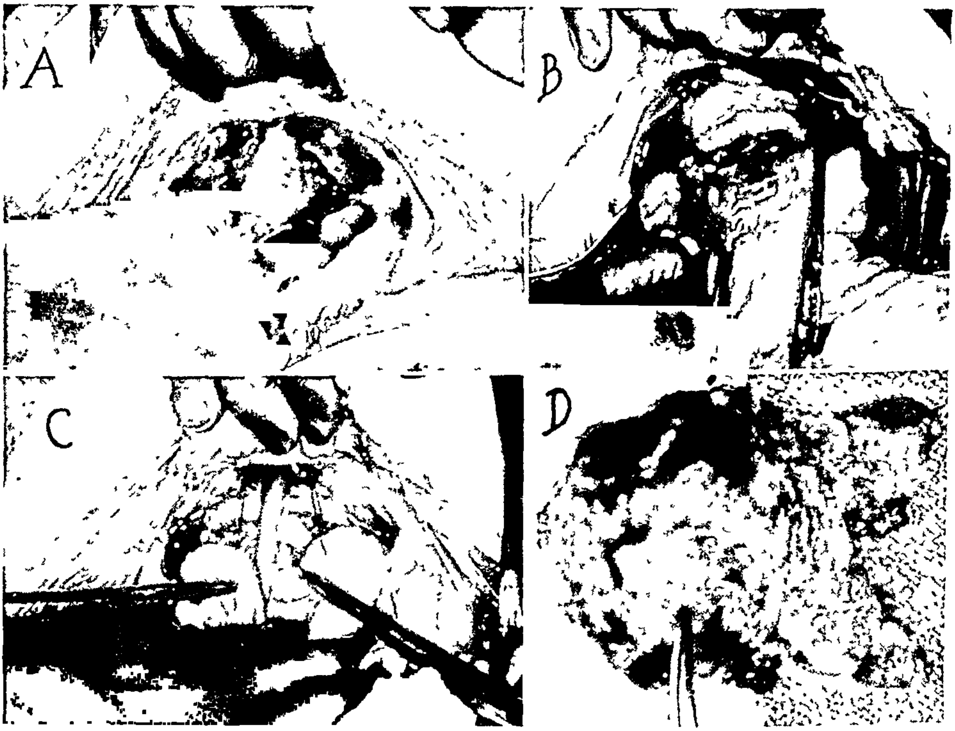

FIG. 4. *A*, exposure of prostate and urethra preparatory to dividing urethra just back of triangular ligament. *B*, prostate and seminal vesicles removed. *C*, stay sutures placed in bladder edge and pulled through on either side of perineum. *D*, specimen showing prostate and vesicles; pointer shows area of biopsy 4 days previously.

vasa deferentia being ligated and cut. Closure of the bladder and re-approximation to the membranous urethra is accomplished by means of a mattress suture through either side of the bladder 1 to 2 cm. above the ureteral orifice. This mattress suture is passed through the floor of the perineum on either side of the urethra. These long mattress sutures of chromic catgut are tied over a button or small piece of gauze on each side of the perineum and just lateral to the bulbous urethra. Tightening of these sutures brings the edges of the bladder down into approximation with the perineal portion of the pelvic floor (fig. 4). This type of anastomosis was first shown to us by Dr. Lytle Atherton of Louisville, Kentucky in 1949. A Foley bag catheter is left in the bladder for drainage and to aid in preservation of continuity of the urethra at the point of anastomosis. One or more sutures may be placed transversely to aid in closing the upper part of the bladder. It is also our custom to place another smaller Foley catheter by a stab wound in the dome of the bladder and bring it through a stab incision in the skin above the suture line. This latter suprapubic drainage catheter is a safety valve in case of unexpected bleeding or if continuous irrigation is found advisable. Healing after removal of this catheter is rarely prolonged more than 24 hours.

RESULTS

In 17 patients deemed suitable for radical prostatectomy by this method we have 3 patients alive and free from demonstrable cancer after 6, 5½ and 5 years respectively, 9 other patients alive after intervals of 2 months to 4 years. It is reasonable to assume that probably one half of these will die from cancer. Four patients died with metastatic cancer after an average interval of 23 months following operation. One patient died of pulmonary embolism 7 days after operation. Four patients suspected of having prostatic cancer on the basis of rectal palpation were found upon open perineal biopsy not to have malignant prostatic disease and further operative procedure was not done. Observation follow-up on these patients has not revealed error in diagnosis after an interval of 1 to 3 years.

SUMMARY

In patients suspected of having early cancer of the prostate the combining of open perineal biopsy with radical retropubic removal 3 to 5 days later for those with proven positive microscopic carcinoma appears to have certain advantages over other approaches or combination of methods. Necessary criteria for radical total prostatectomy are met with minimum chance for error.

Technical advantages of the retropubic approach are found to be enhanced by the previous dissection of the rectum from the prostate at the time of the perineal biopsy. Complete removal of the seminal vesicles is easier and more surely accomplished.

A small series of cases is reported.

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ANDROGEN, GONADOTROPHIN AND STEROID EXCRETION IN MAN BEFORE AND AFTER CASTRATION AND ADRENALECTOMY

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There is in progress in the urologic section of the Peter Bent Brigham Hospital a long term, joint project with the surgical and metabolic units to study: 1) the hormonal changes in the aging normal male subject, 2) the endocrine environment in which carcinoma of the prostate arises and grows, and 3) the endocrine changes that follow hormonal therapy, orchiectomy and adrenalectomy. It is within the scope of this paper only to report certain studies in the latter group. This project has been possible because of the co-operative assistance and advice of both the medical and surgical services of this institution.

Huggins' rationale for orchiectomy in prostatic cancer was removal of testicular androgenic substances thought to promote neoplastic growth.[1] Almost simultaneously Herbst reported the effect of estrogens on prostatic tissue.[2] Other workers have continued to use this treatment to produce pituitary inhibition and to diminish androgen production. When it was found that re-activation of prostatic cancer after initial regression was the regular occurrence Huggins and Scott turned to adrenalectomy to remove the body's remaining androgenic tissue.[3]

The specific changes in hormonal balance achieved by castration and adrenalectomy as well as the accompanying metabolic alterations are complex. Estrogenic and androgenic substances have been isolated from both testis and adrenal cortex. Urinary metabolic degradation products quantitated by chemical and animal assay methods after hydrolysis and extraction are yet the standard indices of the endocrine state; their limitations must be recognized.

Read at annual meeting, American Association of Genito-Urinary Surgeons, Shawnee-on-Delaware, Pa. May 26–28, 1954.

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The authors are indebted to Dr. Richard A. Carey, the Armour Laboratories, for providing H. P. ACTHAR GEL for this study.

This work was done in the Surgical Research Laboratories, Peter Bent Brigham Hospital, Department of Biology Harvard School of Dental Medicine and the Medical Metabolic Laboratories of the Peter Bent Brigham Hospital. The authors acknowledge with gratitude the advice and help of Drs. F. D. Moore and G. W. Thorn.

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METHODS AND TECHNIQUE

Methods of study have included colorimetric estimation of 17-ketosteroids[4] and 17-hydroxycorticoids,[5] and biologic assays of androgenic activity using the chick comb technique,[6] follicle stimulating hormone excretion has been measured by using the mouse uterine weight technique[7] All determinations have been done on 24-hour urines collected on ice Although it has been assumed that urinary 17-ketosteroids are the end-products of androgenic substances, there is recent evidence that they may arise also from other sources such as 11–17 oxysteroids[8] Since it is the true androgenic potency of these hormones which is of greatest interest in prostatic cancer, the actual biological assay of urinary androgens has been carried out This consists of quantitation of the response of the weight of the comb of the immature chick to direct application of urinary extract by comparison with responses of chicks treated with standard androsterone solution and comparison with control chicks Approximately fifty chicks are used for each assay, each urine is assayed at least in duplicate This complex and tedious procedure is carried out in the Biology Laboratory of the Harvard School of Dental Medicine

DISCUSSION AND RESULTS

The study of androgenic excretion has proceeded in several ways One group of subjects was tested for the effect of castration on the levels of androgen Urinary androgenic activity after castration comes from extragonadal sources, presumably the adrenal cortex The control androgen excretion of three patients with prostatic carcinoma ranged from 8 to 13 international units per 24 hours, which is in the low normal range for their ages All showed a drop of at least 35 per cent after castration as shown in table 1

Administration of ACTH in large doses to castrates generally produces a rise in androgen excretion Following 25 i u ACTH, administered intravenously or its equivalent as intramuscular gel, four such patients all showed elevations of 100 per cent or more, as illustrated in table 2 Further investigation of this phenomenon using smaller doses of ACTH in normal as well as castrated males has shown that there may be considerable individual variation in sensitivity of the adrenal cortex to ACTH, with respect to its contribution to androgen excretion

As a means of studying pituitary activity, follicle stimulating hormone levels were assayed in 24 hour urine collections The usual range for an adult male is 10–25 mouse units/24 hours Two types of experimental evidence support the

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TABLE 1. *Urinary biologic androgens before and after castration in patients with prostatic carcinoma*

Patient	Age	Urinary Androgens International Unit/24 hours	
		Before	After
	years		
W. C.	70	8.1	4.4
A. S.	77	12.4	8.2
F. C.	64	13.0	4.5

TABLE 2. *Urinary biologic androgens in male castrates before and during ACTH stimulation*

Patient	Dose of ACTH/Day	Urinary Androgens International Unit/24 hours		
		Control	1st day	2nd day
E. B.	25 mg. iv.	7.9	16.6	14.6
J. T.	25 mg. iv.	2.8	4.5	10.1
F. C.	25 mg. iv.	4.5	27	
H. T.	80 c.u. gel × 2 i.m.	3.2	5.4	11.5

TABLE 3. *FSH levels in men*

	Intact	Castrated
Number of men	21	8
Number of tests	34	15
Tests, 50 m.u /24 hours	1 (15%)	14 (93%)
Tests. 100 m u./24 hours	1 (3%)	11 (75%)

contention that castration causes an increase in FSH activity. First, comparison of intact and castrated men shows a predominance of high values in the latter group, usually 100 mouse units or more as shown in table 3. Second, 2 patients have been followed with serial determinations before and after castration. Each had a normal low level before the procedure and within a few days afterward, each showed an increase; in one case, the level rose from less than 50 to more than 100 mouse units by the second postoperative day

Interpretation of 17-hydroxycorticoid and 17-ketosteroid levels in these patients must judge the effect of operative trauma and the disease as well as loss of the testes. A transient small rise in 17-hydroxycorticoid excretion has been noted on days immediately following castration, an effect frequently associated with mild trauma. The question of the effect of castration on 17-ketosteroid excretion has been studied by others, notably Scott and Vermeulen who found an initial decrease and subsequent rise to and above control levels.[9]

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[9] Scott, W. W. and Vermeulen, C.: Studies of prostatic cancer; excretion of 17 keto-steroids. estrogens and gonadotropins before and after castration. J. Clin. Endocrinol., 2: 455, 1942.

TABLE 4. *Urinary 17 ketosteroids before and after castration*

Subject	Age	Mean 17 Ks mg./24 hr. Urine	
		Before	After
B. M.	65	5.8	4*
A. L.	74	5.2	3.6*
F. B.	80	12.9	3.6*
H. A.	72	6.4	2.5*
S. W.	73	11.7	7.7*
R. C.	52	8.7	6.0*
S. C.	71	2.5	3.3
W. C.	70	7.1	6.6
A. S.	77	6.1	7.9
E. B.	64	8.2	9.1
F. C.	64	6.4	5.9

* Indicates a definite decrease of more than 25%.

In the present study, the data adduced on 11 patients are presented with the comment that alone they do not warrant a conclusion as to the effect of castration on 17-ketosteroid excretion. Six of the eleven showed a decrease shortly after castration, the other five had no definite change, as shown in table 4.

The 17-ketosteroids represent a group of metabolites of testicular and adrenal cortical origin, some of which have no androgenic activity. Estimation of urinary neutral 17-ketosteroids—the time honored standard procedure utilizing the Zimmermann reaction on extract of hydrolyzed urine—provides limited information of the patient's biological state. Indeed, individuals with the same level of neutral steroid excretion frequently differ greatly in the androgenicity of their urines—a function of the amount of androgenic substance present. Since control levels in prostatic cancer patients are generally low—8 mg. or less per 24 hours—a decrease is difficult to demonstrate.

Attempts to gain more specific knowledge of steroid metabolism in prostatic cancer have been made by several groups; fractionation procedures, usually by paper chromatography, are employed. Birke, Franksson and Plantin[10] recently reported an interesting series of studies of excretion of androsterone and etiocholanolone, the two steroids thought to represent the main urinary degradation products of testosterone. Whereas etiocholanolone is biologically inactive, androsterone is strongly androgenic. The authors report that levels of these substances diminish in urine after castration or estrogen therapy, later rising to previous levels.

Interpretation of the effect of bilateral adrenalectomy in six previously castrated prostatic cancer patients is complicated by the fact that they required maintenance of cortisone therapy which *per se* may contribute to urinary hormone excretion. In addition, all received small doses of desoxycorticosterone and estrogenic hormones. All 6 patients were debilitated and in poor condition as a result of extensive metastatic cancer. In 3 patients in whom biologic androgens were estimated before and after adrenalectomy the preoperative level was low for even an elderly castrate. Adrenalectomy was followed by attainment of a still lower level, less than 2 i.u. The 17-ketosteroids ranged from 1.5 to 5 mg. per 24 hours. The values stated persisted during maintenance treatment of 50 mg. or less of cortisone acetate per day. Withdrawal of cortisone for 5 days did not further lower either androgen or ketosteroid levels. On the other hand raising the daily dose to 300 mg. of cortisone acetate or hydrocortisone acetate resulted in increase in both androgens and 17-ketosteroids. In the usual dose range for replacement therapy there appears to be no increase in androgen excretion beyond the minimal amounts detected when virtually all steroid administration has been stopped. These findings have been presented previously.[8]

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[10] Birke, G., Franksson, C. and Plantin, L. O. On the excretion of androgens in cancer of the prostate. Acta Endocrinol., 15 Suppl. 17, 1954.

The source of urinary androgenic substances and 17-ketosteroids in the cascrated adrenalectomized man when cortisone has been withdrawn is unknown. It is unlikely that the desoxycorticosterone or estrogen used could have contributed more than an infinitestimal fraction. It is felt that exogenous cortisone is metabolized and excreted within a day or two of withdrawal. A possible explanation is the existence of accessory ectopic adrenal cortical tissue.[11] However, 2 patients came to autopsy and no adrenal nor testicular tissue was found. Furthermore, the subjects reported have developed evidence of acute adrenal insufficiency whenever cortisone was withdrawn. In addition ACTH stimulation of these patients produces no response so far as eosinophile fall or increased 17 ketosteroid excretion is concerned which further indicates the absence of any physiologically significant functioning adrenal cortical tissue.

SUMMARY

Urinary androgens determined biologically appear to have been sharply and promptly diminished by castration and to have been still further reduced to a minimal level by subsequent adrenalectomy. On maintenance therapy with cortisone acetate the level of excretion remains as low as when replacement therapy is withdrawn. Although biologic androgens do not disappear from the urine of the castrated adrenalectomized man they are so reduced as to indicate a relationship to the clinical improvement sometimes noted after adrenalectomy for prostatic cancer. It has been shown that the 17-ketosteroids sometimes roughly parallel the biologic androgens in their changes after these surgical procedures and may be used as a rough guide of androgenic activity in the patient. It should be emphasized, however, that derivatives of 11–17 oxygenated steroids which are non-androgenic may be excreted as 17-ketosteroids in urines of low biological androgenicity.[8] Further studies of metabolic changes attendant upon the growth, arrest and re-activation of carcinoma of the prostate are necessary for progress in the management of this disease.

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POTENTIAL HAZARDS OF CORTISONE IN TREATMENT OF PROSTATIC CANCER REPORT OF A FATAL CASE

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It has long been known that prolonged administration of cortisone diminishes the endogenous output of ACTH and that the resultant decrease in adrenal stimulation induces at least temporary atrophy of the adrenal glands[1-6] Since the drug has become widely available for clinical use, many patients with advanced prostatic cancer, no longer controlled by orchiectomy and estrogenic therapy, are being given cortisone

An increasing number of reports of its use in the treatment of this disease are now appearing in the literature Harrison[7] treated 9 such patients with cortisone in dosages of 25 to 37 mg a day for 3 months after initial doses of 100 mg daily for the first 3 days All but one patient experienced an increased sense of well being and were relieved of pain, and one showed a decrease in the serum acid phosphatase blood level, although in none was there any objective evidence of control of the disease Hayward[8] reported a case in which there was an increase in appetite and strength and considerable reduction in pain for 15 months under the influence of cortisone Valk and Owens[9] reported some relief of pain and varying degrees of euphoria following cortisone therapy in 4 patients with widespread metastases, in 3 of the 4 patients the serum acid phosphatase level decreased but the bony metastases were not affected

We have given prolonged cortisone therapy to 12 patients with advanced prostatic cancer after orchiectomy and estrogenic therapy were no longer effective The daily dosage varied from 150 mg to 50 mg , the latter amount being the usual dosage during the past year The most outstanding clinical result observed in these cases has been complete or partial temporary relief of pain, and an increased sense of well being amounting to mild euphoria in some instances None of the 12 patients showed any evidence of regression or control of

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Read at annual meeting American Association of Genito Urinary Surgeons Shawnee on Delaware Pa May 26-28 1954

[1] Ingle D J and Kendall E C Atrophy of the adrenal cortex of the rat produced by the administration of large amounts of cortin Science 86 245 1937

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bony metastases, when present. There has been no indication that cortisone can be expected to increase the life expectancy of any of these patients and there has been no convincing evidence of reduction in the serum acid phosphatase levels. Adverse reactions in the patients who received less than 100 mg. of cortisone a day have been absent. Sodium retention and fluid imbalance did not develop in any of our patients maintained on the smaller dosages.

As experience with use of cortisone accumulates, it is becoming increasingly apparent that the potential hazards resulting from the induced adrenal atrophy following prolonged therapy must be carefully considered in every patient so treated. The possibility of sodium retention or depletion of cellular and serum potassium must always be considered, particularly in patients receiving large daily doses. In such cases it may be necessary to replace this loss by administration of two to three grams of potassium chloride daily. It is now generally recognized that extreme caution and careful supervision are mandatory when cortisone must be given to patients with psychotic tendencies, congestive heart failure, active peptic ulcer, renal insufficiency, tuberculosis, syphilis, diabetes or bleeding tendencies.[10]

Finally, it is now known that death from acute adrenal insufficiency is a possibility after any sudden stress, such as that occasioned by any operative procedure, in patients who have received cortisone within the previous 6 months to 1 year or possibly longer. Apparently, any suddenly increased demand for adrenal cortical steroids resulting from sudden stress can have serious consequences in patients whose pituitary adrenal mechanism has been rendered unresponsive to stress by prolonged use of cortisone. The microscopic changes in the adrenal cortex which seem to result from previous cortisone therapy appear to be a reduction in the lipid content of the cells of both the zona glomerulosa and the zona fasciculata. When this has occurred, eosinophilic granular cytoplasm is seen,[11] the cells shrink and there is usually some decrease in the thickness of the cortex, although there is no apparent decrease in the number of cortical cells. Instead, they appear to be compressed with an increase in the nuclear-cytoplasmic size ratio.

Fraser[12] reported a death from irreversible shock following an operation in which autopsy revealed pronounced adrenal cortical atrophy which had been induced by prolonged cortisone therapy. Salassa and associates[11] reported one death following gastrectomy and another following bunionectomy; in both cases the symptoms were consistent with fulminating acute adrenal insufficiency induced by prior cortisone therapy and autopsy disclosed extremely atrophic adrenals. They concluded that the "shock and anuria that followed operation . . . did not seem commensurate with the uneventful operation and anesthesia that preceded it. The appearance of hypercortisonism and the changes observed in the adrenal and pituitary glands at necropsy constituted the only positive necropsy findings apart from pulmonary edema. They appeared to offer adequate evidence for the assumption that the final shock was due to acute adrenal cortical insufficiency resulting from prior cortisone therapy." Lewis and co-workers[13] also reported a death from irreversible shock 6 hours following an operation on a 20 year old woman who had been receiving cortisone for 5 months.

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Within the past few months we have had one postoperative death at the Ochsner Foundation Hospital in which the clinical course as well as the observations at autopsy were similar to the aforementioned fatal cases.

REPORT OF CASE

A white man 57 years old was admitted to the Ochsner Clinic in March 1950 complaining of symptoms of prostatism for 3 years. Transurethral prostatic resection had been performed elsewhere on two occasions, the last 4 weeks before admission. The slides obtained from both operations showed carcinoma of the prostate, grade 2. Estrogenic therapy had been started after the last resection.

There was no roentgenographic evidence of bony metastasis upon admission, and the acid and alkaline phosphatase blood levels were within normal limits. Estrogenic therapy was continued and the patient was kept under observation. His condition was satisfactory until July 1952, when pain in the back and perineum developed. Four months previously orchiectomy had been performed elsewhere. There was still no evidence of bony metastasis. In addition to continued estrogenic therapy, daily administration of 50 mg. of cortisone was begun; this resulted in some relief of pain. Cortisone therapy was continued intermittently for 16 months with no adverse reaction.

In October 1953, because of urinary difficulty due to local recurrence of the tumor, another transurethral prostatic resection was considered necessary. The patient had been receiving 50 mg. of cortisone every day for the previous 3 months. He was given 200 mg. of cortisone intramuscularly each day for 2 days preoperatively as a precautionary measure. Following operation he received a total of 650 mg. of cortisone by combined oral and intramuscular administration. The patient's condition was satisfactory for the first 48 hours, but then he sustained a sudden circulatory collapse and died despite the usual supportive measures.

At autopsy the adrenal glands (fig. 1, *A*) were found to be extremely atrophic. Their combined weight was 6 gm. There was no evidence of recent or old myocardial infarction. The only other significant findings were those associated with the prostatic carcinoma. There was no pulmonary edema, or evidence of old or recent pulmonary embolism.

Microscopic examination (fig. 1, *B*) revealed atrophy of the cortex and tubular degeneration of the zona glomerulosa and zona fasciculata. The cells of the zona fasciculata were small and showed decreased pigmentation and the lipid substance was absent. There were small foci of leukocytes.

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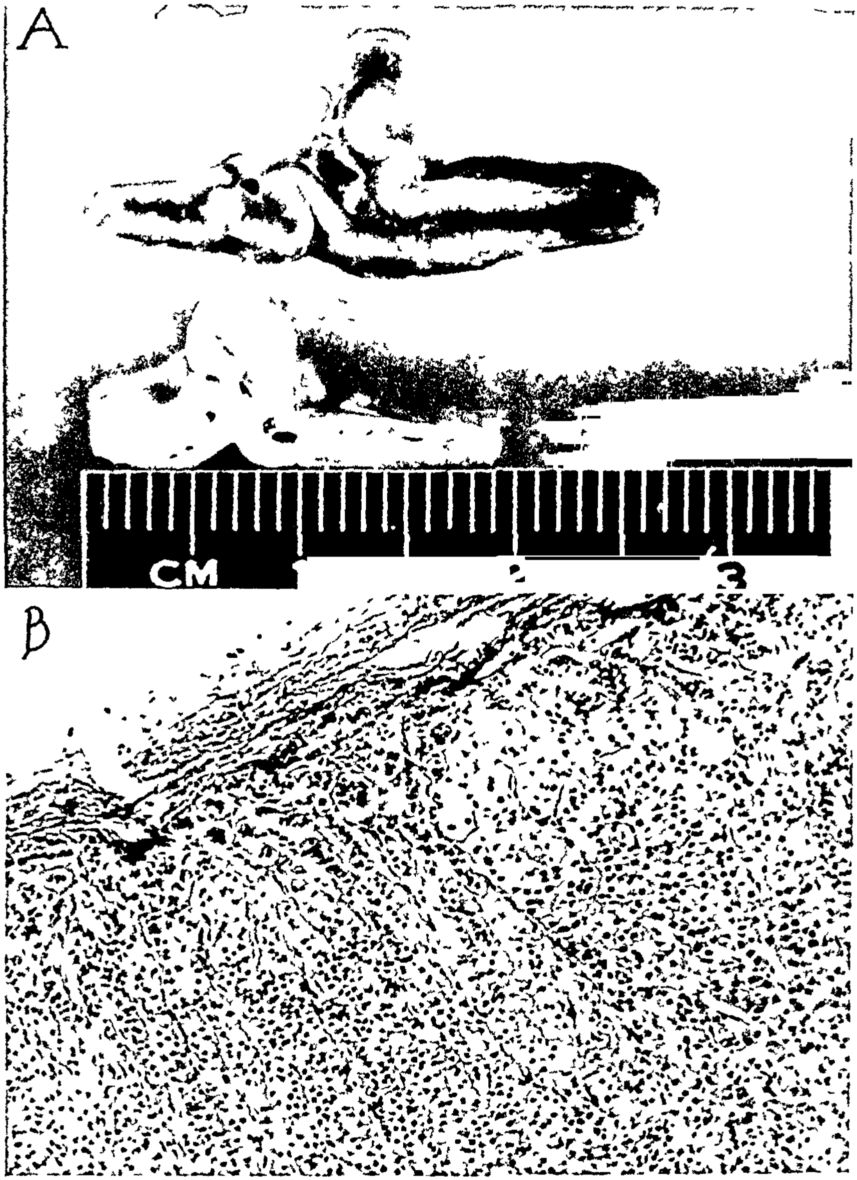

FIG. 1 *A*, gross appearance of adrenal glands compared with normal adrenal gland (shown above) *B*, microscopic appearance of adrenal glands

In this case a relatively innocuous surgical procedure, performed on a patient who appeared to be in good general health, resulted in circulatory collapse and death. The clinical course and subsequent observations at autopsy suggest that acute adrenal cortical insufficiency induced by prior cortisone therapy played a major role in causing death despite attempts to forestall this eventuality by preoperative and postoperative cortisone replacement therapy. This possibility deserves serious consideration in the future in all patients with advanced prostatic cancer receiving cortisone therapy, in whom further palliative prostatic operations are contemplated.

DISCUSSION

In an effort to determine the duration and degree of adrenal cortical atrophy that may be expected from variable amounts of previous cortisone therapy, Salassa and co-workers[11] compared the adrenal glands of 46 adult patients who died of various diseases for which they had received cortisone with those of 42 patients who died of similar diseases but who had not received cortisone. They failed to find either gross or microscopic changes in the adrenals of those patients who had received cortisone for less than 5 days. However, the average weights of the adrenals of those patients who had been treated for more than 5 days were significantly reduced if the cortisone had been continued to within 20 days before death, but in those patients who received no cortisone for at least 21 days prior to death, the average weights of the adrenals had returned to nearly normal. They also noted that in most patients who had received prolonged cortisone therapy there were persistent histologic changes in the adrenal glands even though the combined weight of the glands was within the normal range. These observations emphasize the necessity of anticipating the possibility of acute adrenal insufficiency as the result of any sudden stress in patients receiving prolonged cortisone therapy.

Although various tests for determining adrenal cortical function have been devised, there is no entirely satisfactory test at present that may be employed preoperatively. It is, therefore, extremely difficult from a clinical standpoint, at present, to decide which of these patients is liable to adrenal cortical insufficiency as a result of sudden stress.

The minimal interval that must elapse after withdrawal of cortisone therapy before its depressing effect is completely lost is not known. At present many endocrinologists recommend that any patient having received significant quantities of cortisone therapy for any reason within six months to one year or even longer prior to any contemplated surgical procedure should receive replacement therapy. Endocrinologists are also uncertain as to the shortest period of treatment with cortisone that will induce adrenal cortical atrophy or the minimal daily dosage of cortisone in any given patient which is sufficient to induce adrenal atrophy.

Now that cortisone is so generally and promiscuously used in the treatment of a wide variety of diseases, it is of great importance to determine preoperatively by careful questioning of the patient on whom any surgical procedure is contemplated, whether he has been treated with cortisone, particular attention being accorded those having cushingoid symptoms during treatment, since this is a definite indication of adrenal suppression.

It is currently recommended by many[14] that in every case of anticipated stress, in which there is any doubt as to the patient's adrenal sufficiency, preoperative adrenal hormone replacement therapy be employed prophylactically. At least 200 mg. of cortisone daily should be given intramuscularly for three days prior to operation, and these patients must be carefully observed postoperatively,

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[14] Editorial. Surgery in patients with cortisone induced adrenal insufficiency. J. A. M. A. 148: 1422–1423, 1952.

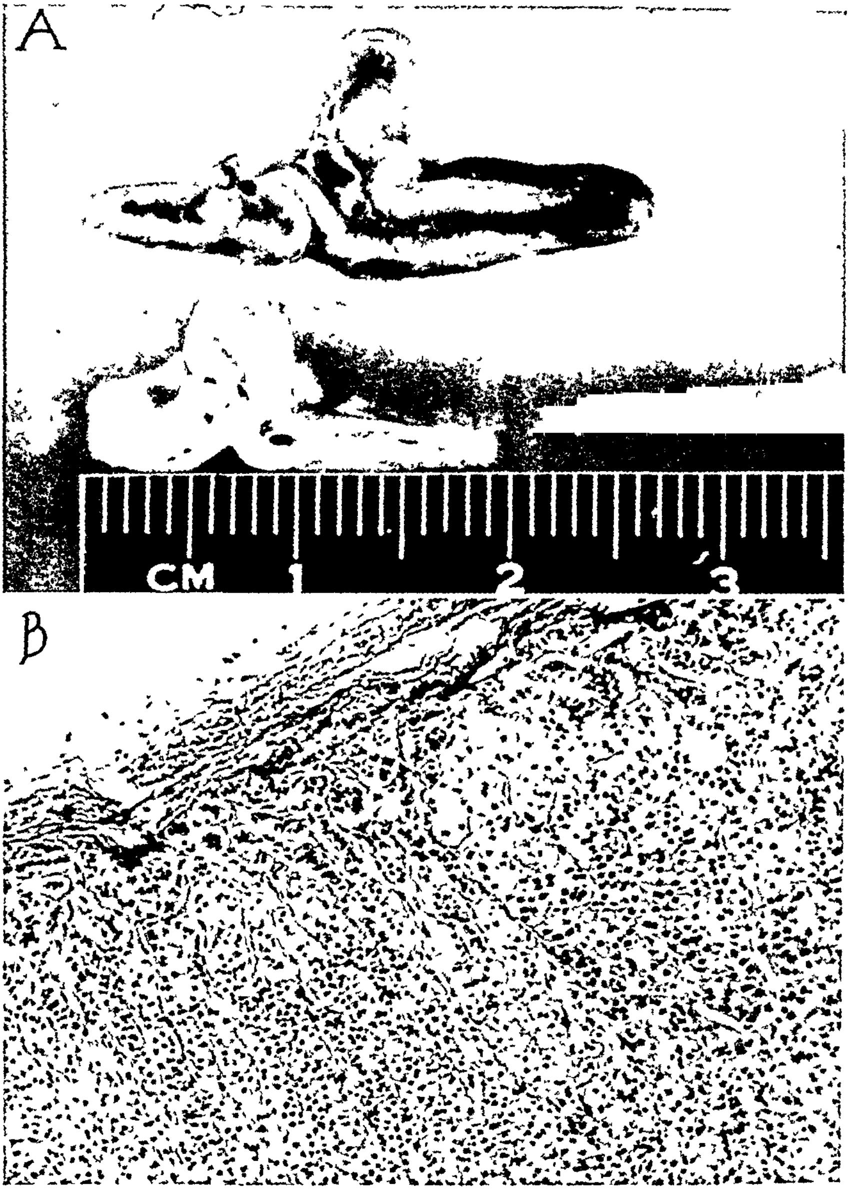

Fig 1. *A*, gross appearance of adrenal glands compared with normal adrenal gland (shown above). *B*, microscopic appearance of adrenal glands.

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SEVENTEEN-KETOSTEROID EXCRETION IN CARCINOMA OF THE PROSTATE

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Investigation of the effects of cortisone and hydrocortisone on disseminated carcinoma of the prostate beginning in 1951 stimulated our interest in the field of steroid metabolism and excretion [1] Our rationale for the use of cortisone and hydrocortisone in patients with relapsing carcinoma of the prostate was based on the evidence first presented by Drs Huggins and Scott that some patients with relapsing carcinoma of the prostate were benefited by bilateral adrenalectomy [2] Soon thereafter numerous reports appeared indicating that adrenal cortical atrophy and insufficiency could and did occur with prolonged or excessive dosage of cortisone [3] [4] At present many clinics have abandoned surgical adrenalectomy in relapsing carcinoma of the prostate because of the short period of palliation that has resulted in most patients We are continuing to treat patients with relapsing carcinoma of the prostate with cortisone or hydrocortisone and estrogen since at least comparable results can be obtained with this therapy During the past 4 months we have stopped using oral cortisone and are now using intramuscular hydrocortisone acetate, 25 mg every other day and 5 mg of stilbestrol orally Munson has shown that in dosage of over 50 mg of cortisone or hydrocortisone orally, significant amounts of urinary androgens are excreted [5] It is his belief that below this level one can accomplish adrenal cortical atrophy medically without exogenous androgen production Conn has also shown that hydrocortisone acetate given intramuscularly produces a decrease of adrenal cortical function as indicated by the fall of 17-ketosteroid excretion [6] This is apparently accomplished without altering the electrolyte or metabolic balance [6] Our early results with hydrocortisone intramuscularly are in accord with this concept We are, in addition, interested in the relationship of the 17-ketosteroid excretion and the clinical course of the patient with carcinoma of the prostate, if such a relationship exists

Urinary 17-ketosteroids are the metabolites of the endocrine excretion of the gonads and of the adrenal cortex The term 17-ketosteroid is attached to this

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Read at annual meeting, American Association of Genito Urinary Surgeons, Shawnee on Delaware, Pa May 26–28, 1954

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Hydrocortisone generously supplied by Upjohn Company

[1] Valk, W L and Owens, R H Effect of cortisone on prostatic carcinoma J Urol , **71** 219, 1954

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group of metabolites because of the occurrence of a carbonyl group at position 17 in the steroid nucleus. A number of steroid compounds are found in the urine. These steroid compounds are of three general types: acidic, derived from the bile-acids; phenolic, from the estrogens; and the neutral steroids which reflect mainly the excretion of metabolic derivatives of gonadal or adrenal cortical hormones. The neutral 17-ketosteroids can be further divided into alpha and beta fractions. Androsterone and etiocholanolone comprise about 70 per cent of the alpha ketonic fraction found in normal urine. Isoandrosterone and dehydroisoandrosterone are found in the beta ketonic fraction. Dehydroisoandrosterone is the main constituent of the beta ketonic fraction. The ratio of alpha to beta ketonic fractions is approximately 9 to 1 in normal individuals.[7] Werner found that there was a daily fluctuation in total androgen or 17-ketosteroid output which was due to variations in the true hormonal or ketonic fraction of the urine.[8] The total 17-ketosteroid output for 24 hours varied from 6 mg. to 14.2 mg. (mean 11.2 mg.) in the males studied in his series. The urinary level of 17-ketosteroid excretion may be affected by a number of factors: a) daily physiologic fluctuation; b) age of the patient; c) the status of the adrenal glands; d) the status of the gonads; e) exogenous sources; f) the status of the pituitary gland and g) systemic disease.[9, 10, 11]

A number of previous studies have been carried out to estimate the urinary excretion of androgens or 17-ketosteroids in carcinoma of the prostate and in patients with benign prostatic hypertrophy. It is important that we differentiate between the studies reported on the excretion of urinary androgen and those on excretion of urinary 17-ketosteroids.[12] The significance lies not only in the type of procedure but also in what is being measured. Urinary androgens are measured by bio-assay which is a specific test for the presence of androgenic hormones. On the other hand, urinary 17-ketosteroid estimation is a chemical assay reflecting the presence of steroids with a carbonyl group at C-17 position. Androgenic substances are only a small part of the total steroid metabolites with a 17-ketosteroid structure.

In 1933 Bühler reported an increase in "free male hormone" in the urine of patients with benign prostatic hyperplasia when compared to normal males of the same age group.[13] In contrast, Rusch and Kundert, in 1937, found a decrease in the urinary androgen in patients with benign hyperplasia of the prostate; however, they compared prostatics with normal healthy young males.[14] In

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[12] Zarrow, M. X., Munson, P. L. and Salter, W. T.: A comparison of androgens determined biologically and 17-ketosteroids determined chemically in urine (normal and abnormal). J. Clin. Endocrin., **10:** 692–702, 1950.

[13] Bühler, F.: Sexualhormonbefunde im Harn von Männern Verschieden Alters. Ztschr. f.d. Ges. Exper. Med., **86:** 650–658, 1933.

[14] Rusch, H. P. and Kundert, P. R.: Hormone excretion in cases of prostatic hypertrophy. J. Urol., **38:** 316–321, 1937.

1940 Moore, Miller and McLellan confirmed the decrease in urinary androgens in prostatics when compared to young healthy males and in addition showed only a slight decrease in urinary androgens in prostatics when compared to normal males of the same age group[15] In the same year, 1940, Dingemanse and Laqueur verified the previous reports of only slight decrease in patients with benign prostatic hyperplasia when compared to normal males of the same age group[16] In 1941 Satterthwaite, Hill and Packard, using the method of Callow, evaluated the urinary output of 17-ketosteroids in 15 patients with prostatic carcinoma[17] Of these they studied 10 cases in which bilateral simultaneous orchiectomy was done for inoperable carcinoma of the prostate This group of patients showed a reduction of 17-ketosteroid output varying from 12 to 60 per cent of the preoperative total They found the mean level of excretion of 17-ketosteroids in patients with benign prostatic hypertrophy did not vary significantly from that for carcinoma of the prostate Of the 15 patients with prostatic carcinoma, the average level of excretion prior to therapeutic procedures varied from 2 3 to 12 6 mg per 24 hours This is within the normal range of variation recorded for elderly men

In 1942 Scott and Vermuelen, in their study of the excretion of 17-ketosteroids before and after castration, found the level of 17-ketosteroids fell in all their cases, post castration[18] They also found that the maximum decrease in 17-ketosteroids occurred 2 to 14 days post orchiectomy in all but one case They further noted that the fall in urinary 17-ketosteroid excretion was not sustained, but rather rose to a higher level than that found prior to castration At that time the duration of this rise in 17-ketosteroids had not been determined Scott also measured the beta fraction of the 17 ketosteroids and found that this fraction fell to a low level after castration In 1942 Miller investigated the urine of patients with benign prostatic hyperplasia and found no abnormal hormones[19] Miller and Moore, in 1942 and again in 1943, reported no essential difference in total urinary androgens between patients with benign prostatic hyperplasia and normal males of the same age group[20] [21] In 1944 Jewett and Frame compared the total urinary excretion of 17-ketosteroids in patients with carcinoma of the prostate with control patients of a similar age group[22] They found no difference in the total 17-ketosteroid excretion between these 2 groups They separated the 17-ketosteroids into alpha and beta fractions in an effort to establish any clinical significance. No significant difference in the excretion of beta 17-ketosteroids between patients with and without carcinoma of the prostate was found. This is also true for a post orchiectomy case where presumably the 17-ketosteroids are derived exclusively from the adrenal cortex. In addition their studies showed no difference in the 17-ketosteroid excretion between untreated cases and patients with carcinoma of the prostate who had been castrated 10 to 24 months previously and in whom there had been a recrudescence of their disease.

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[21] Miller, M L and Moore R A The ratio of urinary androgen and estrogen in relation to benign hypertrophy of the prostate J Urol, 49 861–864, 1943

[22] Frame, L G and Jewett, H J The excretion of 17 ketosteroids in carcinoma of the prostate J Urol, 52 330 333, 1944

In 1948 Brendler and Scott presented an excellent review of the literature concerning the relationship of sex hormones and prostatic disease.[23] In addition, using chromatographic technique for qualitative study as well as colorimetric assay for quantitative study of urinary 17-ketosteroids in patients with prostatic disease they found no qualitative difference in the urinary steroid pattern of patients with benign prostatic hyperplasia, carcinoma of the prostate and normal males in the same age group. They did however, report a difference in the 24-hour urinary excretion of neutral 17-ketosteroids in these three groups. They found those patients with benign hyperplasia show higher values of 24-hour urinary 17-ketosteroids than either of the other two groups. Normal aging males showed the lowest values and those with prostatic cancer fell in between.

In 1949, Robinson and Goulden estimated 17-ketosteroids in urine extracts from 19 normal males ranging in age from 3 to 73 years, urines from 2 cases of benign prostatic hyperplasia and from 6 cases of carcinoma of the prostate.[24] In normal males the amounts of androsterone and etiocholanolone are approximately equal, but in prostatic disease the latter substance is present in relative excess. The authors agree, however, that the difference in the amounts of these substances excreted is probably not actual since they are comparing the absolute excretion of men in the prostatic age group (average age 65 years) with a group of normal, slightly younger men (average age 59 years).

METHOD

The urine specimens for this study were obtained from both in-patients and out-patients. A 24-hour urine specimen was collected in a clean bottle and kept refrigerated during the collection period. The urine was then subjected to hydrolysis with hydrochloric acid and the 17-ketosteroids were determined by the Drekter modification of the Callow method utilizing the Zimmerman reaction.[25, 26]

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[23] Brendler, H. and Scott, W. W.: New diagnostic methods in prostatic cancer: I. Investigation of the chromatographic adsorption technique for qualitative analysis of urinary 17-ketosteroids. J. Urol., **60**: 937–946, 1948.

[24] Robinson, A. and Goulden, F.: A qualitative study of urinary 17-ketosteroids in normal males and in men with prostatic disease. Brit. J. Cancer, **3**: 62–71, 1949.

[25] Drekter, I. J., Pearson, S., Bartczak, E. and McGavack, T. H.: Rapid method for determination of total urinary 17-ketosteroids. J. Clin. Endocrin., **7**: 795–800, 1947.

[26] Callow, N. H., Callow, R. K. and Emmens, C. W.: Colorimetric determination of substances containing the grouping—CH_2CO—in urine extracts as an indication of androgen content. Biochem. J., **32**: 1312–1331, 1938.

Because of the variation in results and the small series reported by these competent investigators, we undertook the accumulation of urinary 17-ketosteroids in all of our aged patients with prostatic disease. As our data accumulated we noted that the 17-ketosteroid excretion was not always decreased in

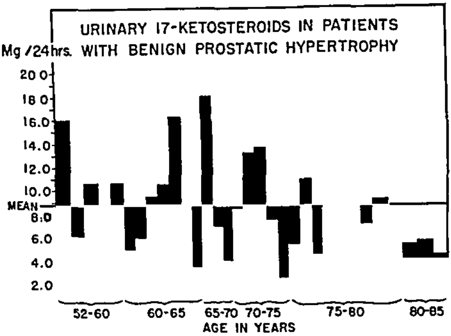

FIG. 1

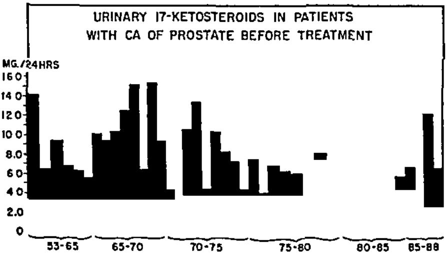

FIG. 2

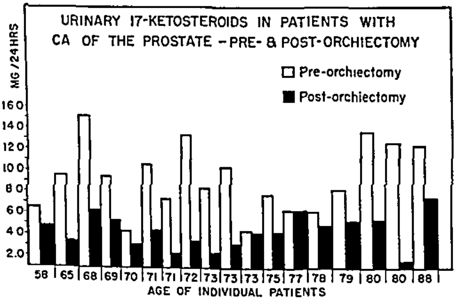

FIG. 3

the aged and that repeated studies in 32 males with benign prostatic hypertrophy failed to reveal any definite pattern of excretion (fig. 1). The mean excretion for this group was 9 mg. per 24 hours. A similar study of 41 patients with untreated carcinoma of the prostate again revealed a wide variation in all age groups (fig. 2). 17-ketosteroid excretion in patients with carcinoma of the prostate pre- and post orchiectomy showed marked decrease in steroid excretion post orchiectomy, varying from 2 to 80 per cent with an average decrease of 30 per cent (fig. 3).

Figure 4 shows individual 17-ketosteroid levels in patients with carcinoma of the prostate orchiectomized 1 month to 5 years previously.

Average urinary 17-ketosteroid excretion in 32 patients with benign prostatic hypertrophy and 41 patients with carcinoma of the prostate was approximately the same with an average of 8.5 mg. of steroid excreted per 24 hours. The average 17-ketosteroid excretion 72 hours post castration in the disseminated carcinoma group was 6 mg. per 24 hours. The late post castration average was 7.8 mg. per 24 hours (fig. 5).

Comparison of initial urinary 17-ketosteroid level with clinical response to cortisone and hydrocortisone therapy failed to give any consistent pattern for prediction of prognosis (fig. 6).

During the past 4 months 8 patients with disseminated carcinoma of the

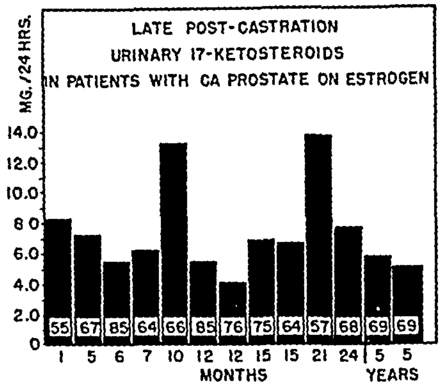

FIG. 4

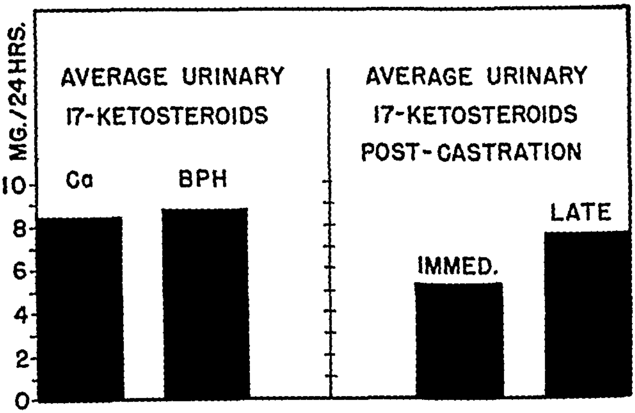

FIG. 5

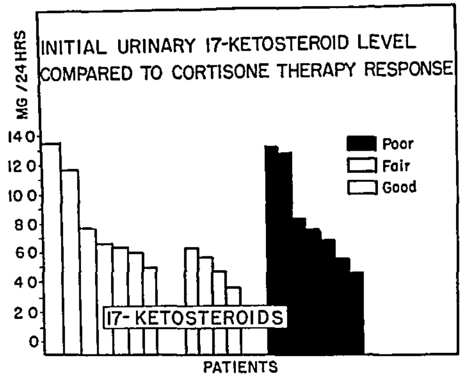

Fig 6

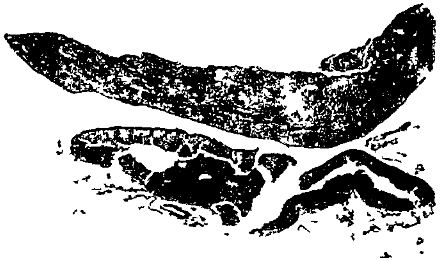

Fig 7

prostate have been given 25 mg of hydrocortisone acetate intramuscularly every other day and 5 mg of stilbestrol orally daily In each of these patients there has been a consistent decrease in the 17-ketosteroid excretion Although it is too early to report the clinical course of these patients, we can say that they appear as well as patients who had received cortisone and estrogen and that the side effects from the hydrocortisone have been nil Adrenal atrophy has been seen in cases that came to autopsy and the photograph (fig 7) shows the right adrenal lying below a prostatic fragment which measures 2 cm in length

Twenty-seven patients with relapsing carcinoma of the prostate have now been treated with cortisone or hydrocortisone and estrogen and to date there have been 9 deaths which can be attributed to lack of control of the carcinoma and 4 deaths from other causes, giving an average survival of 8 4 months to date (fig 8), from the time of clinical relapse Patient C B illustrates well the adrenal cortical suppression produced by hydrocortisone acetate and stilbestrol (fig 9)

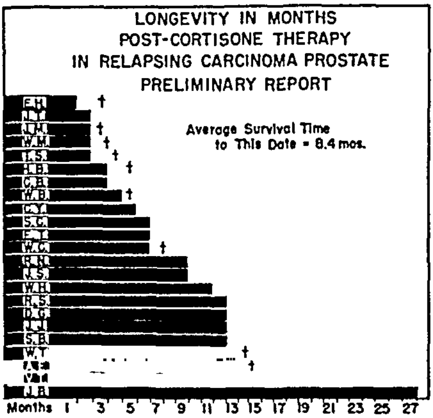

Fig. 8

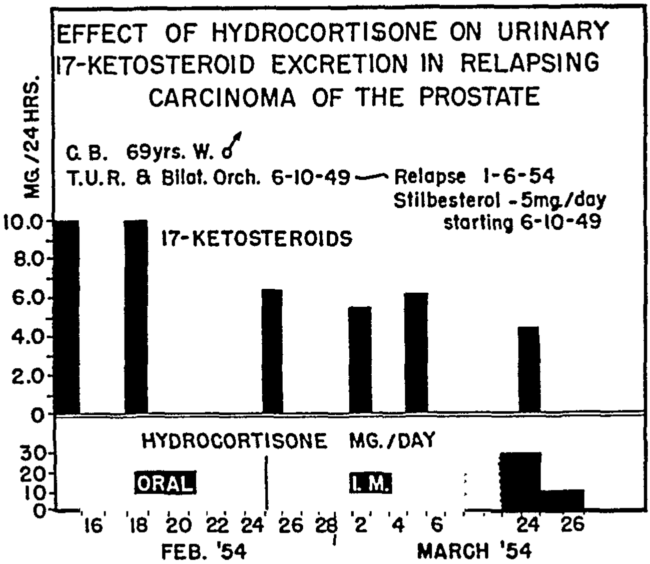

Fig. 9

SUMMARY

Seventeen-ketosteroid excretion in patients with benign prostatic hypertrophy and carcinoma of the prostate shows great individual variation at all ages. The average excretion was, however, the same for both diseases.

There is a marked decrease in 17-ketosteroid excretion 72 hours post castration which is followed by a slow but constant increase in 17-ketosteroid excretion late.

It appears impossible to predict the prognosis of patients with carcinoma of the prostate by determining the initial 17-ketosteroid excretion.

Hydrocortisone acetate given intramuscularly appears to depress the 17-ketosteroid excretion more effectively than oral cortisone or oral hydrocortisone.

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TREATMENT OF TUBERCULOSIS OF GENITO-URINARY ORGANS BY DRUGS

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The purpose of this paper is to review the treatment of tuberculosis of the genito-urinary organs with antibiotics and chemotherapy. It is based principally on the experience of the Research Unit for Genito-Urinary Tuberculosis, Veterans Administration Hospital, Bronx, New York. Dr. John K. Lattimer, of the Department of Urology, has been the urologist in this project. Treatment of patients began December 4, 1946, and has continued without interruption.

Patients with every type of tuberculosis of the genito-urinary organs were treated. They presented the disease in all stages. Diagnosis required either a positive culture or a positive guinea pig examination from the urine. During treatment, cultures were made every 4 months of nine consecutive 24-hour urine specimens. Following treatment, cultures were made every 6 months. When cystoscopic examinations were made, the findings were carefully sketched, life size, on a chart and compared. At each cystoscopy, cultures were made of urine from each ureter. Cultures were made of the bladder urine to show secondary invading organisms, and counts were made of the pus cells in aliquots of each ureteral specimen. At the same time, the bladder capacity was measured. Every 2 weeks, the following laboratory tests were performed: urinalysis, determinations of blood urea nitrogen, erythrocyte sedimentation rate, phenolsulfonphthalein excretion, urine concentration, blood count, total serum protein, and albumin and globulin fractions. Retrograde pyelo-ureterograms were made before treatment was started, immediately after its completion, and every 6 months thereafter. The ureters were catheterized every 4 months during treatment to guard against stricture formation. The streptomycin sensitivity of each positive culture was measured. These procedures, directed principally to investigate the disease in the genito-urinary organs, together with all other necessary examinations, have been continued without interruption through the years. From time to time, additional tests have been added appropriate to changes in treatment.

Close clinical observations were made of each patient. Total bed rest for all was not feasible, but activities were limited to semi-ambulation in the ward. Additional restrictions were imposed on individuals when required. Charts were kept showing each urination and any associated pain or other symptom. Toxic manifestations of drugs were recorded and periodic audiogram and a caloric test were made of each patient. While disappearance of tubercle bacilli from the urine is the most searching test of benefit from treatment, it was, nevertheless, the only criterion used in this research to express arrest of the disease.

Read at annual meeting, American Association of Genito-Urinary Surgeons, Shawnee-on-Delaware, Pa. May 26–28, 1954.

STREPTOMYCIN ALONE

Treatment was first given in 1946, with streptomycin alone at the rate of 1.8 gm. injected intramuscularly daily for 120 days. This drug passes readily into the blood stream after parenteral administration. Between 60 and 80 per cent is excreted in the urine during the 24 hours following its injection. Urinary levels vary with the output of urine; therefore, if kidney function is impaired, high blood and low urine levels result.

Following intramuscular injection, streptomycin passes into the peritoneal and pleural fluids, the fetal circulation, the amniotic and intra-ocular fluids and the bile. It is of clinical importance that it does not diffuse readily into thick-walled abscesses, empyema cavities, or the prostatic fluid and passage from the blood into the cerebrospinal fluid is variable. Absorption from the gastro-intestinal tract is slight; most streptomycin given orally is excreted in the feces apparently unchanged.

Early in the research, immediate benefits from streptomycin were striking but two serious complications were discovered: The drug was toxic to the patients and it produced a specific resistence in the tubercle bacilli. All of the patients who received 1.8 gm. of streptomycin daily showed after about thirty days, by caloric tests, a permanent loss of vestibular function. It was manifested by vertigo which varied in degree from mild dizziness to an extreme in which the patient was incapable of co-ordinated movement. Fortunately, after treatment stopped, the vertigo diminished and, with eye exercises and co-ordination training, practically all of the patients compensated for the ataxia. Injury of the auditory branch of the eighth cranial nerve was not significant in these patients although they were tested every 2 weeks with the audiometer. Skin rashes occurred occasionally when the drug was given in the larger doses and exfoliative dermatitis became so serious in two patients that it was necessary to reduce treatment.

In vitro tests performed before each patient was treated demonstrated that all of the tubercle bacilli were sensitive to streptomycin. Later, however, the organisms from those patients who continued to show tubercle bacilli in the urine while under treatment were found to have increasing resistance to the drug *in vitro*. As far as is known, resistance to streptomycin, once acquired, is never lost.

In an effort to avoid toxicity and increasing bacterial resistence, three other groups of patients were treated with smaller doses of streptomycin and for shorter periods, as shown below. With the dosage decreased, all toxic manifestations were greatly reduced but, at the same time, the effectiveness of the drug against the serious disease was much diminished.

Group 1 was composed of 64 patients. They were given 1.8 gm. of streptomycin daily for 120 days. The drug was injected intramuscularly in doses of 0.3 gm. every 4 hours. At the end of treatment, tubercle bacilli had disappeared from the urine of 81 per cent. After a year without treatment, despite some relapses, 62 per cent of the group continued to excrete normal urine.

Group 2, comprising 42 patients, received 1 gm. streptomycin daily (gm. 0.5

injected every 12 hours), for 120 days. Fifty eight per cent were free from tubercle bacilli when treatment ended but only 46 per cent continued so for more than six months.

Group 3, consisting of 103 patients, received 1.0 gm. streptomycin daily, injected in doses of 0.5 gm. every 12 hours for 42 days. While 50 per cent initially became free from evidence of injection, practically all had relapsed by the end of 6 months.

Group 4, comprising 39 patients, received 0.5 gm. of streptomycin daily for 42 days with little immediate benefit.

It, therefore, became clear that in renal tuberculosis, streptomycin given in doses of 1.8 gm. daily for 120 days produced benefits unapproached by any previous therapy and smaller doses for a shorter period of treatment had a much diminished efficacy.

Tuberculous ureteritis, with superficial ulceration and edema, was improved rapidly by streptomycin. Strictures produced by superficial lesions relaxed rapidly. However, when ureteral strictures were the result of extensive fibrosis, the administration of streptomycin appeared to accelerate fibrous tissue production and decrease further the ureteral lumen.

Tuberculous cystitis, with superficial ulcerations of the bladder mucosa, healed in between four and eight weeks of streptomycin therapy as shown by cystoscopic examinations and biopsies. Frequency and dysuria diminished correspondingly and bladder capacities measurably increased. Fibrous contractures of the bladder wall were not changed by streptomycin.

Prostatic tuberculosis was not significantly improved by streptomycin probably because tuberculous nodules in the gland represent encapsulated caseous material. However, when tuberculous discharges from prostatic ducts produced superficial ulcers in the adjacent urethra and bladder, use of the drug was followed regularly by prompt healing.

Tuberculous epididymitis showed little improvement under streptomycin therapy. This lesion also consists of encapsulated caseous material. Of thirteen epididymal nodules, twelve remained apparently unchanged. When a number of these were resected 18 months after treatment, their centers were still soft and caseous although no tubercle bacilli could be recovered from them by culture.

Draining tuberculous sinuses from tuberculous epididymides persisted until the necrotic focus was removed. On the other hand, discharging sinuses which followed nephrectomy or epididymectomy healed after about three weeks of streptomycin treatment.

Further study and longer observation of patients with renal tuberculosis showed that the results of streptomycin therapy were related closely to the size of the lesion. A classification, therefore, of the patients was made on this basis and the tuberculous processes were described as small, medium, and large.

Small lesions were those which put tubercle bacilli and leukocytes in the ureteral urine but could not be detected in roentgenograms by the most searching techniques. With few exceptions, the urine of these patients was sterilized promptly and, at the end of 7 years, seven of nine showed no relapse.

Medium sized lesions were those in which there was roentgenological evidence of erosion in only one calyx. Two patients out of eight in this group continued to have clear urine for 7 years.

Large lesions indicating advanced renal disease were classified at this time as those which were clearly visible in the pyelogram in two or more calyces. Streptomycin at the rate of 1.8 gm. daily for 120 days temporarily cleared tubercle bacilli from the urine in only 25 per cent of such patients and all of these relapsed by the end of 2 years.

Beyond the fact that streptomycin sterilized the urine of a few patients for as long as 7 years, was the significant observation that during this time there had been no deaths from renal failure even though a number of patients had but a small fragment of a single disease kidney. There was but one death from any cause in this earliest treated group of 25 men. This patient of 60 years succumbed to cardiac failure after his urine had been clear 2½ years. Streptomycin administered for only 120 days, therefore, gave evidence of slowing the progress of renal tuberculosis without damage to kidney function.

STREPTOMYCIN AND PARA-AMINOSALICYLIC ACID (PAS)

Para-aminosalicylic acid (PAS), after extensive use in Europe, especially in Sweden, was found to have a bacteriostatic effect on the tubercle bacillus similar to that of the sulfa drugs. Beginning in October 1948, PAS was combined with streptomycin in a plan of treatment designed to avoid the complications experienced in the use of streptomycin alone.

The bacteriostatic action of PAS, as shown with pulmonary tuberculosis, required prolonged administration because it was necessary to subject the organism to its effects for at least six to eight cell divisions before they could be controlled. On the other hand, streptomycin appeared to produce its full bacteriostatic action after each injection. For these reasons PAS was given in doses of 3.0 gm. 4 times a day and streptomycin was injected at the rate of 1.0 gm. every third day. Thus it was hoped to maintain bacteriostasis for such a long time that the tuberculous process would heal.

The first group of patients received this treatment for 90 days. This was an initial success with 70 per cent which was similar to that which followed use of streptomycin alone. However, following this short treatment, relapse was frequent and prompt. This showed that streptomycin was the more effective of the two drugs and that to control a disease as chronic as tuberculosis of the genitourinary organs with lesions as extensive as those commonly found, treatment of much longer duration was required. Therefore, it was decided to use these drugs in the manner described for a minimal period of one year, and, if pyuria persisted, to prolong treatment indefinitely. This has been found practicable because bacterial resistance to streptomycin and its toxicity are relatively slight in these doses and the nausea or diarrhea from PAS was only occasional and has been further reduced by substituting sodium PAS (fig. 1).

From October 1948, until January 1952, when treatment was again modified, 40 patients received therapy for a year without interruption and were observed for an additional 2 years following treatment. Although all of these patients showed extensive cavernous lesions in roentgenograms when treatment began, 80 per cent were apparently healthy and free from baciluria or pyuria 3 years later.

Soon after beginning this treatment with streptomycin and PAS, the urine cleared in the great majority of patients and remained clear during the year of therapy. Superficial lesions of the ureter or bladder disappeared without strictures forming. Ureteral strictures, the result of much fibrosis, seldom relax and may require cystoscopic dilatation. Prostatic tuberculosis soon showed subsidence of inflammation by endoscopic examination and the urine became normal. At the end of 3 years, prostatic lesions showed absence of active disease in 80 per cent, but the original nodules in the gland usually persisted. Tuberculous epididymitis has continued refractory to medication and can be eliminated surely only by excision. This operation should be preceded and followed by use of the drugs.

Roentgenological evidence of lasting benefit from drug therapy in renal tuberculosis has been difficult to measure although enlargement of cavities has appeared arrested in both small and large lesions when studied in serial pyelograms. Strictures of the calyceal infundibula or ureters may contract so rapidly under treatment that it appears necessary to take excretion urograms every 4 months for their early discovery. Free drainage of the ureters usually can be maintained by adequate dilatation while sometimes a limited excision can be performed to remove a nondraining, chronically infected calyx.

The confinement of patients for a year of treatment may be difficult especially as the great majority feel quite well for the greater part of this time. There is no problem at first when weakness, pain, frequency of urination and dysuria induce the individual to obtain relief by resting in bed. Soon, however, suffering ends, unbroken sleep is possible and a feeling of well being follows. For the first 6

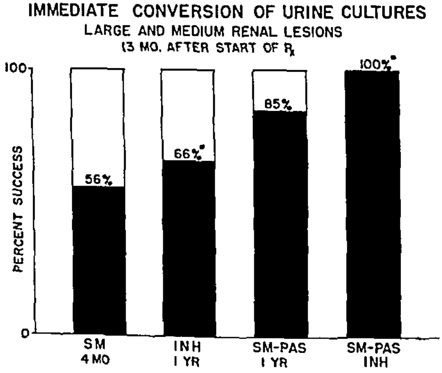

FIG. 1. Combined streptomycin (SM), para-aminosalicylic acid (PAS), and isoniazid (INH) sterilizes urine more surely (right hand column) than use of these drugs individually.

months, activities are limited to the ward and during this time, the many mild diversions provided by social workers are invaluable. After 6 months, greater activity, possibly to the extent of light work, can be permitted the healthier individual.

ISO-NICOTINIC ACID HYDRAZID (ISONIAZID) (INH)

This drug is 600 times more powerful than PAS and apparently as effective as streptomycin in killing the tubercle bacilli in the test tube. It also shows great clinical promise after a short trial.

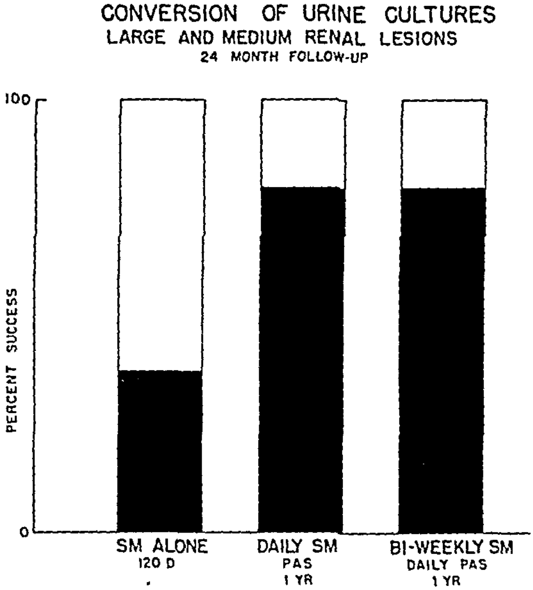

FIG. 2. A year after treatment ended, 80 per cent of the patients treated for 1 year with streptomycin and PAS continued well. Those given streptomycin twice each week (right hand column) relapsed no more than did those treated with SM daily and toxic effects of more intermittent treatment were less.

Like streptomycin, isoniazid brings about a gradual improvement in the cystoscopic appearance of the lesions of tuberculous cystitis and in some patients urine cultures become sterile. It is excellent in streptomycin resistant infections and it is not toxic for the nephrons (fig. 2).

When used alone, however, isoniazid appears to have the same limitations as streptomycin, together with a number of dangers specific to itself. The drug is ineffective in sterilizing the urine from massive kidney lesions with large amounts of necrotic tissue. Resistance to isoniazid may be developed by tubercle bacilli in from two to eight weeks. In fact, spontaneous resistance to 5 mg. per 100 cc was found in four of the first twelve patients treated in this series, even before the drug had been administered. Furthermore, a precaution must be taken with isoniazid which is unnecessary with streptomycin and PAS, because this drug may accumulate in the blood to a serious degree when kidney excretion is impaired. At high blood concentrations, isoniazid may produce hyperreflexia, muscle twitchings, sphincter spasms and serious convulsions. Extremely high blood levels may occur without a proportionate increase in symptoms because hyperreflexia is not an accurate measure of the amount of drug in the blood and thus cannot be used as a danger signal of toxicity. Isoniazid should not be given to epileptics. Sphincter spasm, if it occurs, can be controlled by banthine. In spite of these dangers, the probable benefits of isoniazid should not be withheld from uremic patients with advanced renal tuberculosis but they must be observed closely with frequent blood tests to measure the drug concentration.

DOSAGE AND DURATION OF TREATMENT

Since the best treatment program for isoniazid is as yet unknown, it appears reasonable to base the dosage for each patient on the sensitivity of his tubercle bacilli. This information is obtained before treatment is started.

An adequate, nontoxic daily dose for most patients is 3 mg. per kilo of body weight. This is given in two or three divided doses and produces blood levels of from 1 to 2 mg. per ml. If, however, preliminary studies show resistance of the organisms to 5 mg. or more per ml., the dosage must be increased considerably to attain high peak blood levels. The optimal duration of isoniazid treatment is unknown. Because resistence to this drug, when used alone, can develop within two to eight weeks, it has been found desirable to give it in combination with streptomycin and PAS. All three drugs appear to have different modes of action and when given together for long periods, it appears possible to control the tuberculous infection without producing toxicity.

In an effort to utilize the benefits of all three drugs and avoid their possible complications, a group of patients has been given streptomycin 1.0 gm. twice a week, sodium PAS 5 gm. 3 times daily and isoniazid 100 mg. 3 times daily. This treatment is to continue for a year. At present, the urine of every patient has become clear and their general health has improved but observations have been conducted for little more than a year and are, therefore, without significance.

Another group of patients is in the process of receiving a year of treatment with streptomycin gm. 1.0 twice weekly and isoniazid 300 mg. daily. The period of observation has also been too short although good immediate results were noted.

Still another group is receiving isoniazid plus sodium PAS for one year.

Sodium PAS has proved easier for the patients to take than PAS because with sodium PAS, gastro-intestinal symptoms are less.

Streptomycin has been preferred to dihydrostreptomycin. While the latter drug produces less vertigo, it is followed by much more permanent deafness. Since March 1953, distrycin, a mixture of streptomycin and dihydrostreptomycin has been used with satisfaction. It has the good clinical effects of streptomycin and less toxicity than either drug used alone.

COMBINED DRUG THERAPY AND SURGERY IN RENAL TUBERCULOSIS

It must be remembered that practically all patients with renal tuberculosis, no matter how extensive, under the present protracted treatment soon excrete clear, germ-free urine, improve in general health and show roentgenographic evidence of arrest of the infection. Practically all remain well during treatment.

Following completion of the year's treatment, a certain number relapse, the rate depending principally on the extent of the disease before treatment was started. These patients now resume treatment and can again be controlled promptly because the present regimen with the three drugs avoids the development of drug resistance or any serious toxic effects. Therefore, it may be possible for almost any patient to live indefinitely on medical treatment alone as long as he is closely observed and promptly treated. However, present results in this research show that every patient with a lesion large enough to be visible in a pyelogram must be watched for at least five years for fear he may relapse. This includes almost every patient with clinical renal tuberculosis.

Despite the unprecedented efficacy of the drugs in inhibiting the disease, its complete removal whenever possible continues to be considerably more desirable. Surgical excision is the only known way to eradicate fibrocaseous necrotic tuberculous lesions. Recommended therapy, therefore, as of 1954, in carefully proved unilateral renal tuberculosis is still nephrectomy. This operation should be done with the patient's infection controlled by medical treatment because the drugs always help significantly. The improved general health of the patient will better fit him for the operation, and with the lesions partically arrested and the urine sterilized, there should be less danger of infecting the wound or disseminating the organisms to produce miliary or meningeal tuberculosis.

Ideal drug therapy to assist nephrectomy consists of a 6-month course of streptomycin 1 gm. every 3 days, sodium PAS 15 gm. daily, and isoniazid 300 mg. daily. On the day of operation and on the first three postoperative days, give streptomycin gm. 0.5 every 6 hours and PAS gm. 20 every 12 hours by infusion. Follow the operation by at least 6 months of continuous therapy with the three drugs, just as before the operation.

Attempts to obtain all possible benefits from intensive medical treatment for a short time have proved disappointing, but there is a place for concentrated treatment for short periods; for instance, to quickly prepare a patient for surgery or to quickly get an extremely ill patient under drug control, give streptomycin gm. 0.5 every 6 hours, PAS gm. 20 every 12 hours by infusion and isoniazid 100 mg. 3 times a day for one week. Thereafter, treat the patient with the 3 drugs for a year.

No nephrectomy of choice should be performed on either kidney when both are tuberculous. The pressing problem with such patients is to conserve as much functioning renal tissue as long as possible. Present medical therapy appears to do this successfully. Occasionally, intractable pain or sepsis necessitates removal of one kidney when both are tuberculous. For such patients, as much preoperative drug therapy as possible is recommended, with postoperative treatment for at least a year. This should be followed by continuous observation and further treatment in the event of relapse.

Following the success of Semb in resecting tuberculous portions of kidneys when the infection was controlled by drugs, the operation of partial nephrectomy became an accepted procedure in this research unit. During 1951, Lattimer successfully resected tuberculous lesions from the kidneys of five patients receiving streptomycin and PAS. Description of the careful selection of patients based on detailed preoperative studies, the operation and postoperative treatment will not be given here. While fewer than 5 per cent of the patients examined were suitable for this operation, discovery of a medical regimen which makes such operations practicable is highly significant.

SUMMARY

Streptomycin, given alone in intramuscular doses of 1.8 gm. daily for 120 days to patients with tuberculosis of the genito-urinary organs, produced prompt relief of all symptoms and clearing of the urine in 80 per cent. A year later, 62 per cent remained well.

All patients who were given 1.8 gm. of streptomycin daily suffered permanent loss of vestibular function after about 30 days and an increasing bacterial resistance to the drug soon developed.

Smaller doses and shorter treatment periods reduced these complications but, at the same time, the benefits from treatment were diminished.

Para-aminosalicylic acid (PAS), bacteriostatic for the Mycobacterium tuberculosis in doses of 3 gm. 4 times a day, permits the amount of streptomycin to be reduced to gm. 1.0 twice weekly. This combined treatment, continued without interruption for a year, produced improved therapeutic results with no serious complications.

Under this treatment symptoms promptly subsided, general health improved, organisms and leukocytes disappeared from the urine and serial pyelograms showed arrest of the lesions.

Observations made following treatment showed that relapse was most likely to occur in patients with lesions sufficiently extensive to produce visible deformities of the renal pelvis or calyces. Resistance to drug control and promptness to relapse following treatment appeared to depend on the extent of the lesion.

If relapse occurs, the patient should resume treatment for at least another year.

The only proved cure for fibrocaseous necrotic tuberculous lesions, at present, is surgical excision. After the disease has been controlled by prolonged drug therapy, nephrectomy is recommended for proved, extensive, unilateral renal tuberculosis. Postoperative treatment should be given for at least 6 months. With the same preoperative and postoperative medical protection, tuberculous epididymides should be excised.

Similarly, utilizing the disease-arresting results from a long period of drug therapy, localized tuberculous lesions have been removed by partial nephrectomy. While this is a practicable operation, fewer than 5 per cent of the patients with renal tuberculosis have satisfied the necessarily searching criteria of suitability.

Iso-nicotinic acid hydrazid (isoniazid), a drug apparently similar in its action to streptomycin and far stronger in the test tube than PAS, may produce possibly serious complications. Since it has great clinical promise, it has been added to the present treatment plan. This consists of a year of uninterrupted treatment with streptomycin gm. 1.0 twice weekly, sodium PAS 5 gm. 3 times a day and isoniazid 100 mg. 3 times a day. Although all 20 patients who received this treatment responded promptly and favorably, insufficient time has passed since treatment ended to measure the results accurately. However, use of these drugs has produced striking local and systemic improvement in patients with tuberculosis of the genito-urinary organs in all stages. These benefits have been derived without demonstrable injury to the renal function.

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THE CHANGING FLORA IN URINARY INFECTIONS IN THIS ANTIBIOTIC AGE

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Approximately two-thirds of the general population have been exposed to antibiotics at one time or another and one-third have received sulfonamides, according to K. Riley. She stated that 864 people out of 1200 questioned had received penicillin.

This universal use of antibiotics has brought about a notable change in the flora found in the urinary tract infections. This alteration affects both prognosis and treatment to such an extent as to justify recording some of the specific changes noted.

The most obvious change is the increased resistance of the coccal infections to penicillin. When penicillin was first introduced Fleming, Raumelkamp, and Maxon reported high activity of penicillin against most strains of both coagulose positive and negative staphylococci *in vitro* in 1941. Spink reported 88 per cent of the species inhibited.

Today the picture is very different. Of 58 Micrococcus organisms isolated from our clinical cases only 3 were found sensitive to penicillin or 5 per cent.

The bacteriologist of the Massachusetts General Hospital, Dr. L. Kunz, reported through a personal communication from Dr. Walter S. Kerr, Jr. that out of 119 Micrococcus organisms isolated in that clinic in September and October 1953, only 31 were sensitive to penicillin or 26 per cent.

The presence of coccal infections resistant to oxytetracycline and chlortetracycline is on the increase but to a lesser degree. Organisms found to be resistant to penicillin are not necessarily so to oxytetracycline and chlorotetracycline. Organisms resistant to oxytetracycline are also resistant to chlorotetracycline. This is also the case concerning tetracycline.

The presence of such a high number of coccal organisms resistant to penicillin is not due to increased resistance. C. B. Chain has shown that "two types of staphylococcus exist, one of them penicillin-sensitive, and the other naturally resistant to penicillin." He demonstrated that the "penicillin resistant strains produce an enzyme called penicillinase that destroys penicillin." The absence of such protective phenomena in the gonococcus probably explains why penicillin is still so effective.

One of the most serious consequences of the emergence of penicillin resistant Micrococcus is the development of ulcerative enteritis. Thirty-seven deaths have been reported in the literature. A modified expression of this condition and some-

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This study was aided by funds from the Olin Foundation carried out in St. John's Hospital [illegible] Brennan and Miss Ruth Jacques.

Th [illegible] Company.

Ch [illegible]

Chloromycetin is the trade mark for the antibiotic chloramphenicol and was supplied by Parke Davis and Company.

times not recognized is its manifestation of diarrhea, weakness, and gaseous distention. Chester W. Fairlie and Ralph E. Kendall report this condition as caused by the overgrowth of the resistant Micrococcus organisms but emphasize that other factors may enter into the problem since systemic toxic effects such as hypotension and azotemia are also present.

BACILLARY INFECTIONS

In bacillary infections, the survival of the more resistant organisms is quite apparent. There is a noticeable increase in B. proteus and Pseudomonas infections. In 1949 and 1950 B. proteus was found in 12 per cent of our patients. In 1952 and 1953 B. proteus had increased to 16 per cent. The Pseudomonas increased from 16 per cent in 1949 and 1950 to 32 per cent in 1952 and 1953. In the pre-antibiotic period all the organisms except B. proteus and the Pseudomonas constituted 72 per cent, whereas in the antibiotic age of 1952 and 1953 all the other organisms constituted only 52 per cent.

This poses a growing serious problem and makes it highly important to not only determine the sensitivity test by the disk method but also to identify the organism. It becomes equally important to know how best to treat these stubborn organisms.

TREATMENT OF MICROCOCCUS INFECTIONS

The realization that a high percentage of coccal organisms now causing infections are resistant to penicillin makes the routine administration of penicillin or combiotic as a prophylactic measure inadvisable. We have long since discontinued this practice.

The clinical and laboratory experience with erythromycin would suggest that it should be the drug of choice in coccal infections at the present time. Our studies at St. John's Hospital indicate that 80 per cent of the Micrococcus organisms isolated in our urinary infections were susceptible to erythromycin and, as previously stated, only 6 per cent of these same organisms were sensitive to penicillin.

Of the Micrococcus organism cultures in the Massachusetts General Hospital 97½ per cent were sensitive to erythromycin and only 26 per cent to penicillin. It would, therefore, seem reasonable to state that erythromycin should be the drug of choice in Micrococcus infections. The same comparison has been noted in other coccal infections; that is, the pneumococcus and the enterococcus (Streptococcus faecalis).

A patient with endocarditis and septicemia caused by the enterococcus illustrated some features. Shortly after a retropubic prostatectomy a low grade fever, elevated sedimentation rate of 68, and a positive blood culture of enterococcus on three occasions, together with a heart murmur, established a diagnosis of endocarditis with septicemia. The laboratory findings are interesting. The disk test showed no inhibition to penicillin but was sensitive to erythromycin. This would then suggest that penicillin would be ineffective in this case. However, the tube dilution test indicated that the bacteriostatic end point of penicillin was 6.25 units per cubic centimeter (potassium salt of penicillin) and the bacteriostatic end point of ilotycin was 0 487 micrograms per cubic centimeter (ilotycin base) The bactericidal end point of penicillin was 50 units per cubic centimeter and ilotycin 12 5 micrograms per cubic centimeter This would indicate that the ilotycin was superior to the penicillin in both the bacteriostatic and bacteriocidal end points, but it does indicate that with a very high dosage of penicillin the organism could be killed This patient was given high doses of erythromycin intravenously and by mouth, resulting in complete recovery

The successful clinical effect of penicillin, despite negative inhibition recorded by the disk method, is explained by the very high blood level attainable with penicillin and emphasizes the necessity of high doses of penicillin in some cases

High blood levels can be obtained also by erythromycin According to Kirby, et al, by giving 500 mg of erythromycin every 6 hours, blood levels of 20, 30, and 50 micrograms per milliliter can be obtained This is comparable to the penicillin blood level attained by giving 2 to 3 million procaine penicillin units daily When it is realized that only ½ microgram per milliliter is sufficient to inhibit most staphylococci, erythromycin should be a most effective drug

Oxytetracycline and chlortetracycline cannot attain this high blood level and are bacteriostatic rather than bactericidal

It is probable that with the widespread use of erythromycin the Micrococcus will become resistant to it, in fact, a report from an Ohio community in which erythromycin had been used for three months indicated an increasing number of erythromycin resistant coccal infections

TREATMENT OF BACILLARY INFECTIONS

B proteus is best treated by furadantin, chloromycetin and gantrisin acetyl This is borne out by our study which indicates that of 81 B proteus organisms, 66 were inhibited by chloromycetin, of 40 sensitivity tests, 34 were inhibited by furadantin, of 110 sensitivity tests, 76 were inhibited by gantrisin Tetracycline, oxytetracycline and chlorotetracycline are of little practical value against B proteus since they inhibit only about 7 per cent

Pseudomonas found in clinical cases today is resistant to most of the drugs, polymyxin B being the exception In our study 118 Pseudomonas organisms were inhibited by polymyxin B out of 149 sensitivity tests performed However, the nephrotoxic and neurotoxic symptoms limit its use We wish to offer a new solution to this problem

After the combination of streptomycin and oxytetracycline proved effective in a stubborn case, we administered this combination to 52 patients with Pseudomonas infections Forty-two were controlled, 8 of which recurred, but 34 remained clinically and culturally recovered It is interesting to note that the *in vitro* sensitivity studies by the tube dilution test demonstrated no increase in the combination over the individual sensitivity of each drug However, the blood taken from an individual who has been given streptomycin and oxytetracycline when added to the test tubes with Pseudomonas did cause inhibition This would suggest that something in the blood augments the synergistic action of these drugs

To date it would appear that this combination is the one of choice in persistent Pseudomonas infections.

CONCLUSIONS

A change in the flora found in urinary infections today is produced by the universal use of antibiotics. This is demonstrated by the emergence of resistant strains of the Micrococcus, these strains being protected from the antibiotics by the production of penicillinase when exposed to penicillin. Only a small percentage of Micrococci are now found sensitive to penicillin. Erythromycin has proved to be a favorable substitute for penicillin.

The micro-organisms found in bacillary infections are predominantly B. proteus and Pyocyaneus due to the survival of these species. The other bacillary micro-organisms appear less frequently because they were more susceptible to the antibiotics universely used. It is necessary to identify these resistant organisms since the drug of choice varies according to the species found. The Pyocyaneus is best treated with the combination of oxytetracycline and streptomycin. B. proteus is best treated with furadantin, chloromycetin, and gantrisin.

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FATAL AIR EMBOLISM DURING UROLOGIC OPERATION

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The medical literature records one or more instances of pulmonary air embolism, usually fatal, occurring in association with the following procedures: 1) vaginal insufflation and douching during pregnancy; 2) cesarean section; 3) antral irrigation; 4) attempted self-abortion; 5) tubal insufflation; 6) urethroscopy with air-inflating urethroscope; 7) intentional introduction of air into cavities or potential cavities, such as the pleural cavity, peritoneal cavity, retroperitoneal or perirenal spaces, bladder, joint cavities, paranasal sinuses and eustachian tube; 8) operations on the breast, thyroid, lungs and prostate; 9) blood donation; 10) blood transfusion; 11) high altitude flying; and 12) deep sea diving.

In a bibliography of more than sixty papers, only 5 reports relating to the subject of air embolism in urologic conditions have been found (Campbell and Work; Dible, et al.; Jeck; Mathé; Weyrauch). We thought it was interesting that no report of air embolism following retrograde air pyelography appeared.

The purposes of this paper are 1) to point out certain common factors relative to the pathogenesis of air embolism; 2) to present a case of fatal air embolism due to a previously unreported etiologic situation; 3) to suggest a preventive measure that may be employed to prevent air embolism in further situations of the kind reported; 4) to discuss certain extremely important factors that have not yet found their way into the urologic literature which relate to the mechanisms of the cause of death from air embolism; and 5) to furnish a comprehensive bibliography on the general subject.

The term "sucking of air" is used rather loosely in the literature to account for the initial stage in the production of air embolism, and is mentioned here largely to challenge its use. Normal venous pressure ranges between 40 and 110 mm. of water. Except in certain rare circumstances when a vein is opened at a gravity level well above that of the right auricle or in certain procedures in or about the chest where negative venous pressures occur as the result of respiratory movements, veins just do not and cannot "suck" air. Careful comparative study of the reported cases of air embolism will show that the one common denominator in the pathogenesis of this condition is *pressure on the air* either during or after its introduction into some extravascular part of the body.

In Campbell and Work's case of fatal air embolism following suprapubic prostatectomy, reported in 1947, the authors did not have an opinion satisfactory to themselves as to why the embolism occurred; however, their protocol records that drainage tubes became obstructed by a blood clot at about the same time that the patient went bad. The obstruction was relieved promptly, but it would take only an instant for air trapped in the bladder behind the obstructed tube to be forced into the venous circulation if the patient coughed or strained in any other way.

Read at annual meeting, Southeastern Section of American Urological Association, Palm Beach, Fla. April 12-15, 1954.

In Dible's cases of air embolism associated with urethroscopy and tubal insufflation; in Mathé's classic report and in Jeck's report, both of which concern air embolism associated with distention of the bladder with air as a step in the suprapubic operative approach to the bladder; and in Weyrauch's report of air embolism following perirenal insufflation, *air pressure in excess of venous pressure* has been the one common denominator.

Dr. Mathé's report which appeared in 1929 deserves special mention. He was the first to point out the danger of inflating the bladder with air to facilitate the suprapubic surgical approach to the bladder, and he advised the substitution of "harmless sterile water or mild antiseptic solutions" for this purpose. Dr. Mathé's is a scholarly and comprehensive summary of the entire subject of air embolism at that time and records 31 cases of air embolism following injection of air into some part of the urinary tract for diagnostic or operative reasons reported either in the literature or to him personally. His report affords an extensive bibliography of the older literature which is not included here. Without exception, all of the case reports recorded by Dr. Mathé indicate that the air that caused the embolus was under *pressure greater than that of normal venous pressure.*

CASE REPORT

A 52 year old Negro was admitted to the Halifax District Hospital early in December 1949 in desperately ill condition due to the extravasation of urine up the anterior abdominal wall from a ruptured urethra. The urethra had been ruptured by the instrumentation of urethral strictures in another office about 2 days previously.

The patient was taken promptly to the operating room for multiple incisions and drainage of the anterior abdominal wall, groins, and perineum, and for suprapubic cystostomy. After a somewhat stormy course he made a satisfactory recovery from his acute illness, and he was discharged from the hospital about 6 weeks postoperatively with his suprapubic tube functioning well. After repeated attempts, a filiform finally was passed through the strictured urethra, the urethra was dilated with followers, and a catheter was inserted. The patient wore this catheter for approximately 2 weeks with excellent dilatation of his strictures, and the suprapubic tube was removed and the fistula was curetted.

Although the urethra was kept dilated through a 26F sound and antibiotics and chemotherapeutics were used freely, the patient's suprapubic fistula repeatedly broke down and drained and his urine remained heavily infected. These difficulties were found to be due to bladder neck obstruction from early benign prostatic hyperplasia and from contracture of the vesical neck.

The patient was re-admitted to the hospital early in May 1950 and transurethral resection of his bladder neck obstruction was carried out without difficulty.

By this time he had so much infected tissue about his suprapubic fistula that it was felt that excision of this inflammatory tissue and operative closure of the fistula were necessary for the complete rehabilitation of the patient. This operation was carried out on May 10, 1950, approximately six months from the time of his original, acute urinary extravasation. We did not have a urethral catheter in place since the open suprapubic fistula as well as scarring precluded distention of his bladder. An elliptical incision was used to excise the inflammatory tissue down to the bladder. The various tissue planes were developed by sharp and blunt dissection. The bladder was closed tightly with interrupted catgut sutures and the remainder of the wound was closed in layers. Two rubber wick drains were left down to the rectus fascia. When the closure was started, the anesthetist began letting up on the patient's anesthesia and, as the last skin sutures were being placed, the patient reacted involuntarily to the painful stimulation and struggled against his restraints. As the dressings were being applied the anesthetist noted a sudden, rapid change in color and found the patient pulseless. Artificial respiration with 100 per cent oxygen, intravenous coramine, and intracardiac adrenalin were given without effect and the patient was pronounced dead. No one at the time of death had any idea why death had occurred, except that it seemed obviously to be a cardiac death of some kind. Autopsy was obtained which showed that the vena cava and right side of the heart were filled with frothy blood and that the cause of death was air embolism.

DISCUSSION

There is nothing much more frustrating to a surgeon than to have a patient concerning whom he is very happy one minute dead on the operating table a minute later and for no obvious reason. We were most fortunate to have an autopsy done promptly on this patient, since the true cause of death had not occurred to any of us. In retrospect it is quite easy to see how air was trapped in the bladder (fig. 1) the walls of which were held open to a certain extent by perivesical scarring and induration, and forced into the venous circulation at the end of the operative procedure by increased intra-abdominal pressure when the patient was straining.

In order to prevent such an unhappy occurrence in similar situations since that time, we first close the bladder opening tightly about a small Robinson catheter; any air in the bladder is evacuated and replaced with sterile water or saline through the catheter which then is withdrawn and the wound is closed in layers.

We have found no reference to the exceptionally practical experimental work of Durant, Long and Oppenheimer in the urologic literature and it needs to be mentioned here. These investigators, working with dogs, found four factors to be most closely related to mortality from air embolism. These factors are: 1) the amount of air injected, 2) the speed of injection of the air, 3) the position of the individual getting the air, and 4) the effectiveness of the pulmonary excretory mechanism.

The position of the individual is an extremely important factor and one which these authors were first to point out. They found that an animal can tolerate more air intravenously when lying on the left side than can be tolerated in any other position. They further found that if an animal is allowed to develop evidence of marked right ventricular failure from air embolism while lying on his back and then is turned onto his left side, recovery frequently follows immediately. Conversely, the right lateral position is by far the worst possible position for the animal.

Open chest experiments by the investigators revealed the explanation for the recovery of these animals when turned into the left lateral position. These experiments showed that the right ventricle labors against the obstruction of an air trap in its outflow tract when the position of the animal is such as to make this outflow tract the most superior portion of the right heart. Such would be the case with the animal on his back or right side. When the animal is turned on the left side, however, the outflow tract assumes a position inferior to the body of the right ventricle; the air trap then rises away from this now inferior position of the outflow tract and, presumably, is churned into a froth which is mixed with the blood in the right ventricular cavity and gradually is passed by the now unobstructed right ventricle to the lungs where it can be excreted. The left lateral position also was shown to increase the efficiency of the excretion of embolic air by the lungs.

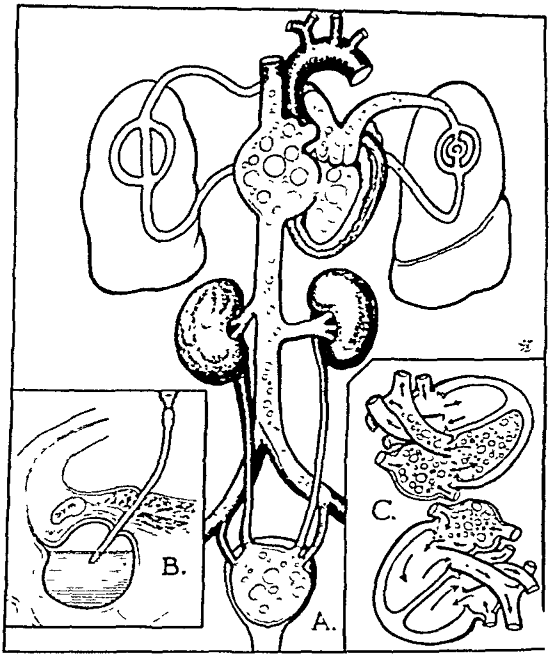

FIG. 1. *A*, schematic representation of passage of air from bladder cavity into venous circulation and thence to right heart and lungs; *B*, evacuation of air from bladder and its replacement with water or saline in closing suprapubic cystostomy; *C*, above, heart in right lateral position, allowing air to pass freely into pulmonary conus and form an air trap, below, heart in left lateral position, causing air trap to rise away from now inferiorly positioned outflow tract of right ventricle.

We are reliably informed by colleagues in other fields of medicine and surgery that a number of lives have been saved by the application of these facts disclosed by Durant and his co-workers, namely, by the simple expedient of turning the patient onto his left side whenever air embolism is suspected and keeping him there until the air has been eliminated. We only wish that we had known what we know now about this problem when we were faced with the emergency reported to you earlier with our own patient, and that we might have had the good judgment to recognize the true nature of the situation and to apply these principles

SUMMARY

Fatal air embolism of the venous or pulmonary type has been reported to occur in association with a wide variety of procedures

Pressure in excess of venous pressure on the air either during or after its introduction has been the one common denominator in nearly all the reported cases of fatal or near fatal pulmonary air embolism

A case of fatal air embolism due to a previously unreported etiologic situation is presented and simple, specific, preventive measures that can be taken are mentioned

The work of Durant and associates, showing that the left lateral position may be lifesaving for patients with pulmonary air embolism, is reviewed

We are indebted to Dr Arthur Schwartz of Daytona Beach whose careful postmortem study disclosed the cause of death in the case reported, and to Mrs Claire Price King, Daytona Beach, and to Mr Carl Bishop, Department of Pathology, Duke Hospital, for the illustrations

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SIGNIFICANCE OF ADRENAL ENLARGEMENT CAUSED BY ESTROGEN TREATMENT

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Since the work of Huggins and his associates[1] which demonstrated the beneficial effect of castration and/or estrogen therapy in individuals having prostatic cancer, there has been acceptance of the androgen theory in the etiology of this neoplasm It has long since become standard management to treat these men by castration and with estrogens, either singly or in combination The survey analysis of a large series of patients treated by the three methods (Nesbit and Baum[2]) showed statistically that a combination of castration and estrogen therapy, both initiated at the time of diagnosis, results in a greater percentage of 5-year survivals than does treatment by castration alone or by estrogen therapy alone Despite this demonstrated advantage, however, most urologists have been prone to initially utilize only one of these means of treatment because of the almost invariable recrudescence of the neoplasm at varying periods following the initial response of the tumor It has been an almost universal experience that utilization at this point in the course of the disease of either castration or estrogen therapy (depending on which was previously instituted) will result in a second remission of symptoms and tumor activity This remission is usually followed after variable periods of time by a second reactivation of the tumor That bilateral adrenalectomy at this time will result in clinical improvement, as demonstrated by Huggins and Scott,[3] has led to the belief that the recrudescence of the neoplastic process is due to androgens produced by the adrenal glands Further evidence to support this assumption is the fact that, although 17-keto-steroid urine excretion levels fall following bilateral orchiectomy, there is a secondary rise to levels in excess of precastration levels Concomitant with the clinical improvement in cases of prostatic carcinoma following bilateral adrenalectomy, there is a disappearance of 17-ketosteroids from the urine

Because of the above facts, it has been thought that the recrudescence of prostatic cancer following the improvement with castration and estrogen therapy is due to androgen production by the adrenals For this reason, considerable interest was recently aroused by the report of Thompson and Werner (1951)[4] that the administration of a new synthetic estrogen, TACE (chlorotrianisene), does not result in enlargement of the adrenals and pituitary of the rat It has been demonstrated that there is enlargement of these organs in rats treated with

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pharmacological doses of natural estrogens (Greep and Jones;[5] Lynch[6]) and by other synthetic estrogens.[4]

On the assumption that the increase in weight of the adrenals might result in an increased production of androgen, Smith, Rush and Evans (1951)[7] have recommended the use of TACE in preference to stilbestrol or natural estrogens in the treatment of men having prostatic cancer.

To test the validity of the above assumption, it was decided to attempt, in our laboratory, to demonstrate in the rat whether the enlarged adrenals resulting from injections of natural estrogens do or do not secrete an increased amount of androgen.

It was further proposed to study the effect of prolonged estrogen administration on the testes, prostate, pituitary and adrenals of the rat in order to determine whether the changes induced in these organs are reversible. In a previous communication from this laboratory[6] it was shown that there is complete recovery from testis and prostate atrophy and from adrenal enlargement in rats subjected to three weeks administration of estrogen, although there is persistent pituitary enlargement nine weeks after cessation of therapy.

MATERIALS AND METHODS

Experiment 1. Although it was realized that the cockerel comb method affords the most sensitive test or assay for androgens, it was decided to use the prostate weight in the estrogen treated rats as an indicator of androgen production by the enlarged adrenals. It was felt that, even though minute amounts of androgen might not result in prostatic growth, yet any really significant increase in androgen production by the adrenals should result in prostatic enlargement above the normal castrate weight.

Young adult 200 gm. male albino rats of the Wistar strain were castrated and then divided into two groups. The rats in one group were injected every third day with 0.5 mg. of estradiol benzoate in sesame oil* for a period of 24 days, a course of treatment which had previously been demonstrated to cause the adrenals to approximately double their normal weight. The other group of animals received no treatment and served as castrate controls. Groups of the treated animals were sacrificed at periods of 1, 2 and 5 weeks following cessation of estrogen therapy and the wet weights of the prostate, combined adrenals and the pituitary were recorded. The animals in the control group were sacrificed simultaneously with the last group of the estrogen treated animals. All organs were weighed to the nearest milligram using the Roller-Smith microtorsion balance.

Experiment 2. Young adult 200 gm. albino male rats of the Wistar strain were injected twice weekly for a period of 3 months with 0.5 mg. of estradiol benzoate, a dosage presumably analogous (correcting for life span and body weight) to a dosage of about 50 mg. daily in a 150 pound man. This dose was not selected as

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[5] Greep, R. O. and Jones, I. C.: Recent Progr. Hormone Research, 5: 197, 1950.

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* Estradiol benzoate in sesame oil labeled Progynon-B was provided by The Schering Corporation through the courtesy of Dr. Edward Henderson.

TABLE 1 *Body weight recorded in grams. All organ weights recorded in milligrams. Each figure is the average for that group*

	Body Weight	Anterior Prostate	Posterior Prostate	Total Prostate	Paired Adrenals	Pituitary
Group 1. Pre treatment (6 rats)	233			502	32	7
Group 2 One week after cessation of treatment (3 rats)	237			58	51	23
Group 3. Two weeks after cessation of treatment (3 rats) ..	252			55	69	20
Group 4. Five weeks after cessation of treatment (9 rats)	265	28	26	54	62	19
Group 5. Castrate controls (6 rats)..........	320	23	29	52	37	14

TABLE 2. *Individual weights of animals in group 4 from table 1*

	Body Weight	Anterior Prostate	Posterior Prostate	Total Prostate	Paired Adrenals	Pituitary
Group 4. Rat 1	310	18	20	38	84	20
Rat 2	220	52	40	92	62	12
Rat 3	270	20	28	48	60	32
Rat 4	280	36	30	66	56	20
Rat 5	285	32	28	60	62	18
Rat 6	225	30	24	54	48	12
Rat 7	255	22	22	44	62	21
Rat 8	265	24	22	46	75	18
Rat 9	280	20	22	42	50	18
Average	265	28	26	54	62	19

being in either the physiologic or pharmacologic range. Rather was it selected because it was the smallest dose which had produced an appreciable and consistent degree of testis atrophy in a three week period.[8] A group of 6 animals was sacrificed prior to initiating the injections and a similar number of both treated and untreated animals were sacrificed at intervals during the treatment period, at the end of this period, and at intervals thereafter, the last group being sacrificed thirty weeks after cessation of the estrogen therapy. The body weight and the wet weights of the paired testes, the prostate, the pituitary and the paired adrenals were recorded.

RESULTS

Experiment 1. As in previous experiments, the 4 weeks of estrogen therapy resulted in a marked increase in adrenal and pituitary weights. The adrenals continued to increase in size after treatment was discontinued, attaining a peak average weight of 69 mg. 2 weeks after cessation of therapy, as compared with the average pre-treatment average weight of 32 mg. As shown in experiment 2, three months of estrogen therapy induces no further enlargement.

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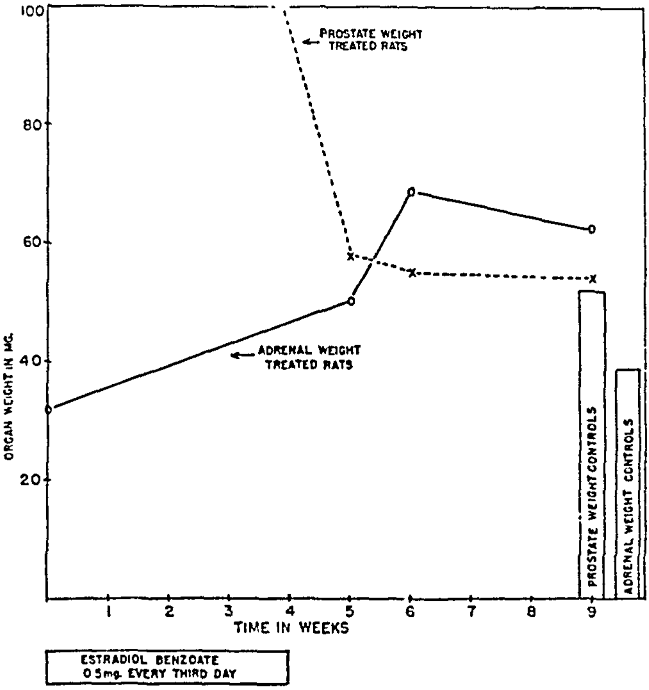

Fig. 1

Table 1 gives a tabulation of the average weights of the prostate and adrenals in the different groups. There is no significant difference in prostate weight between the estrogen treated animals and the castrate controls. At the peak of the adrenal enlargement 2 weeks after cessation of estrogen therapy, the average prostate weight was 55 mg. as compared to an average prostate weight of 52 mg. in the castrate controls. The largest individual pair of adrenals in the treated rats, weighing 84 mg. (table 2, rat 1), was associated with a prostate weighing only 38 mg. These data are shown graphically in figure 1.

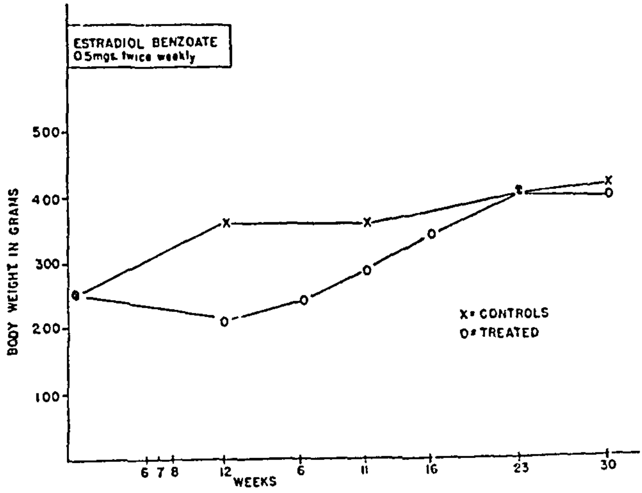

Fig. 2

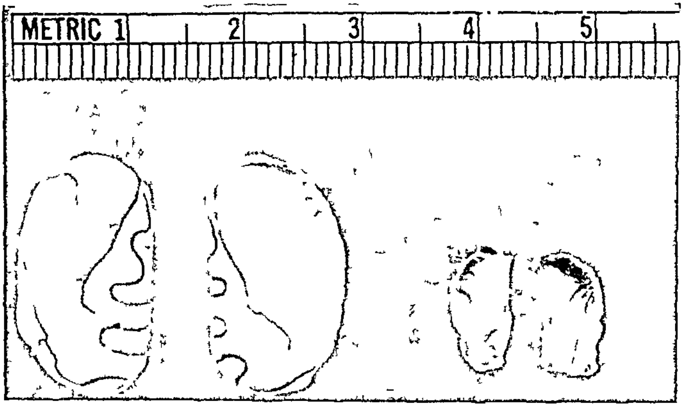

Fig 3 Photograph of testes from a normal and a treated animal at end of 3 months of estrogen therapy Note marked atrophy in estrogen treated animal

Experiment 2 Body weight: Figure 2 shows the usual failure of the estrogen treated animal to gain weight at the same rate as the untreated animal when administered doses in the pharmacologic range This effect was no longer evident 23 weeks after treatment was discontinued

Testis weight· The weight of the paired testes at the end of the treatment period was 3 2 gm in the control animals and 0 30 gm or 9 4 per cent of the control weight in the treated animals The contrast in size is illustrated photographically in figure 3 As the graph (fig 4) demonstrates, there was persistence

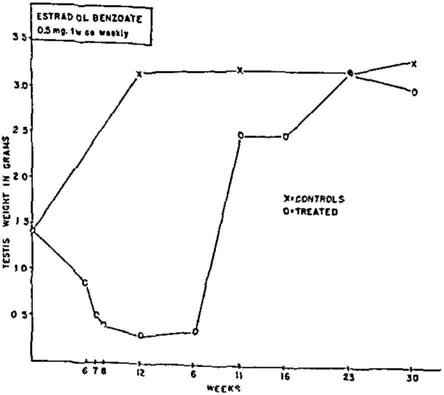

Fig 4

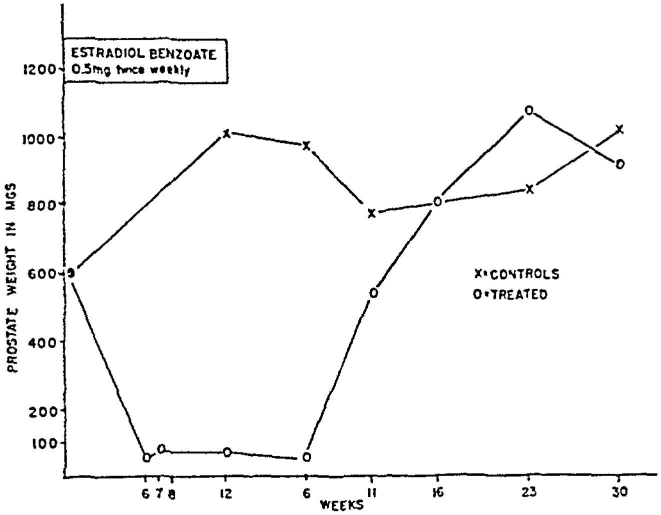

FIG. 5

of the atrophy for a period of 6 weeks and total recovery of normal weight in 23 weeks.

Prostate weight: Figure 5 shows the prostatic atrophy which persisted for a similar period of 6 weeks, the prostate regaining normal weight 16 weeks following the cessation of the therapy. That the prostate regained control weight prior to the testes indicates that the Leydig cells recover at a more rapid rate than the germinal epithelium of the tubules, which was expected, inasmuch as it is believed that estrogen inhibits the production of LH or ICSH by the pituitary to a lesser degree than FSH.

Pituitary weight: Figure 6 shows the five-fold enlargement of the pituitary resulting from estrogen administration. This still persisted in a diminished, yet significant, degree 30 weeks later.

Adrenal weight: Figure 7 shows the adrenal enlargement induced by the estrogen therapy and its persistence at a significant level 30 weeks later.

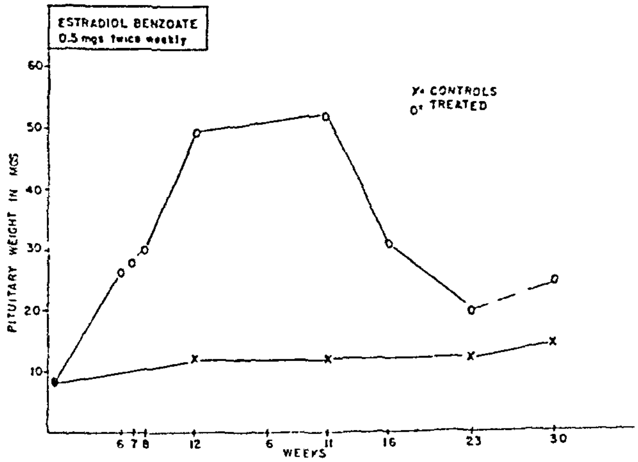

FIG. 6

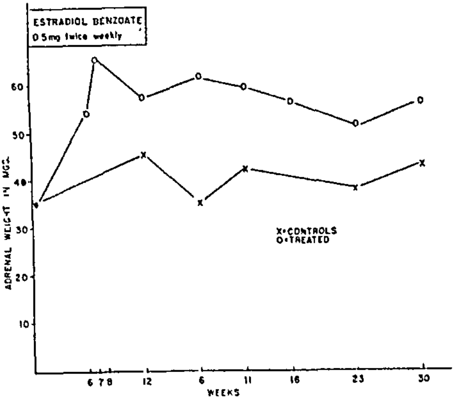

FIG. 7

DISCUSSION AND CONCLUSIONS

Experiment 1 affords no support for the theory that the enlarged adrenals in estrogen treated animals produce an increased amount of androgen as suggested by Smith, Rush and Evans.[7] In regard to the adrenal production of androgens following castration, Scott[9] states that this question "remains unsettled in the normal animal and man." Evidence cited against increased androgen production was that of Richter and Uhlenhuth[10] who observed that whereas the adrenals of the wild rat showed considerable hyperplasia after castration, the seminal vesicles and prostates of these animals remained atrophic. Sayers,[11] likewise cited by Scott, concluded that "adrenal cortical androgens are not likely to have an important role in man, since the compensatory increase in androgen production, if it does occur, is not of sufficient magnitude to prevent the development of deficiency symptoms following castration."

One must be careful to observe that the foregoing evidence deals with the laboratory animal and the normal human male, and not with individuals having prostatic cancer. We should not forget the strong clinical evidence afforded by the improvement of such men following bilateral adrenalectomy. At this time, it can be concluded only that further investigation must be made of the role played by the adrenals in individuals suffering from inoperable prostatic cancer.

Consideration of the data provided by *experiment 2*, while leading to no definite conclusions, seems to justify the following suggestions for clinical application.

1) While no evidence has been forwarded to support the hypothesis that the enlarged adrenals caused by estrogen therapy produce increased amounts of androgen, yet the fact that the natural estrogens, and the synthetic estrogen

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[10] Richter, C. P. and Uhlenhuth, E. H.: Personal communication to Scott.[9]
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widely in use, cause pituitary and adrenal enlargement, would seem to indicate that the use of TACE, which does not, would be preferable. Comparable clinical results following administration of this new synthetic estrogen in a large series of patients with prostatic cancer will obviously be required to justify this supposition. The report of Smith, Rush and Evans[7] concerning its beneficial effect in cases of prostatic cancer is encouraging.

2) The question is often raised as to whether one is justified in using estrogens in the treatment of mumps orchitis and in phalloplasties. In *experiment 2* there was complete functional recovery of the rat testes even after 3 months of intensive estrogen therapy. The testes were normal in weight, demonstrated normal Leydig cell function by maintaining the prostate at normal weight and, on microscopic examination, showed normal spermatogenesis. Concerning the human, little information is available. In the discussion of a previous communication,[6] Charny cited 3 men he had treated with estrogen. One was a man who had been arrested on four occasions for criminal rape. He was given 5 mg. of estrogen daily for 30 days. At the end of therapy, semen examination showed azospermia and testicular biopsy revealed degeneration of the germinal epithelium. Another biopsy done eight weeks later showed complete regeneration of the tubules. The other two men were cases of oligospermia who were treated with estrogen until there was a disappearance of sperm from the semen. Examination several weeks later showed a return of sperm at a level above the pretreatment level.

On the basis of these meager data concerning the human, we are not able to conclude that estrogen may be used with impunity in the young human male, although our animal studies indicate that it can be.

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STUDIES IN UROLITHIASIS: III. PHYSICOCHEMICAL PRINCIPLES IN STONE FORMATION AND PREVENTION

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The results of at least four independent studies have converged to produce evidence which may be built into a logical and consistent (if incomplete) theory which partially explains the formation of urinary calculi and provides information of value in treatment

These studies may be enumerated as follows:

1) The work of Meyer[1] in determining the conditions which govern precipitation of stone forming substances in the urine,

2) The metabolic studies on experimental urolithiasis in rats by Hammarsten,[2]

3) The observations by Randall on stone formation in the human kidney,[3] and

4) Our own crystallographic study of the structure and composition of some 6000 urinary calculi with clinical correlations in the cases of selected patients from whom calculi have been obtained

As a result of this study it seems pertinent to consider some principles of physical chemistry which bear upon calculus formation and prevention, with particular emphasis upon the importance of the stone nucleus and the factors underlying stone growth

The present project began some years ago as a study of urinary calculi from the standpoint of crystal structure The reader is referred to previous papers[4, 5] for a description of the techniques used, the nature and occurrence of the crystalline constituents, the structure and composition of nuclei, et cetera Only a brief statement will be made here

Because urinary calculi are crystalline it is possible to study them with the same techniques which are used in the study of minerals These methods are examination of powdered calculous material by polarized light with a petrographic microscope, and 2) study by x-ray diffraction photography Using these methods it has been possible to study the origin and structure of calculi and to identify crystalline material in the tissues of the kidney, even when present in microscopic amounts

In addition, the examination of urinary calculi with the polarizing microscope has provided a very practical method for the accurate and rapid identification of

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[3] Randall A The initiating lesions of renal calculus Surg , Gynec & Obst , 64 1-8, 1939 Randall A The origin and growth of renal calculi Ann Surg , 105 1009–1027, 1937 Randall, A The etiology of primary renal calculus Reports of the VII Congress of the International Society of Urology, part 1, pp 186–261, 1939

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the components of urinary calculi, including the nucleus and the various layers. The opportunity to correlate stone structure and composition by an intimate and simultaneous study is possible only with this technique. One may instantly identify all the crystalline substances present in a portion of powdered calculus; nothing is missed. The first portion of the stone formed, which is called the nucleus, is believed to be of causal significance. As will be explained later, the presence of a nucleus is believed to facilitate stone growth. This nucleus is often very small and may then be identified only by optical study. The preponderant crystalline substance present in the stone may be of entirely different composition than the nucleus. In such a stone the composition of the nucleus may be entirely missed by chemical analysis or it may be reported as a "trace" with no statement as to its significance.

It should be stated that a few laboratories do provide an acceptable chemical analysis of those calculi which are of simple structure; most do not. In stones of mixed composition such reports are usually offered as a confusing list of the separate ions or radicles present. Crystallographic analysis reports the composition of the stone in terms of the compounds present in the various parts of the stone, including the nucleus. It would seem that a report which listed the compounds present in each part of the stone, from nucleus to outermost layer, had much to recommend it. The value of the additional information made available by crystallographic study as compared with the results of an *accurate* chemical analysis is unknown at present. Conceivably it may hinge in part upon whether knowledge of the composition of the nucleus (as determined by crystallographic study) is found to be of real value in stone prevention programs.

We are frequently asked about the identification of calculi by spectroscopic techniques. It is possible to identify the components of calculi by these methods within certain technical limitations which will not be discussed here. But accurate analysis of many calculi of complicated structure demands scrutiny of the internal portion of the stone, sometimes under magnification, so that nothing will be missed. In a stone of complicated structure several samples must be run by these techniques to identify the components. It is so much simpler to instantly identify all the components under the petrographic microscope.

Analysis of urinary calculi is important. Since kidney stones are prone to recur in probably 15–20 per cent of all cases it is advisable to seek preventive measures when possible. A knowledge of the chemical composition of the stone may help us determine the cause so that we may eradicate this cause in addition to removing the stone. A knowledge of stone composition is also of value in setting up regimens of medical management to prevent recurrence in cases in which continued preventive measures are necessary. In recurrent calcium-containing stone one looks for a cause for hypercalcinuria, such as hyperparathyroidism, post-menopausal osteoporosis, acidosis, Cushing's syndrome, immobilization, or excessive calcium intake. Unfortunately all too often we are unable to find a cause for the increased urinary calcium excretion. If the calculus contains magnesium in its central portion one may usually postulate a urea-splitting infection as causal instead of hypercalcinuria, and direct treatment accordingly. (See later.)

CLASSIFICATION OF CALCULI

There are apparently *only 3 important crystalline substances in calcium-containing calculi*. They are calcium oxalate monohydrate, calcium phosphate (or apatite as it has been called) and magnesium ammonium phosphate. In addition, uric acid and cystine are of clinical importance.

These clinically important substances in calculi will be briefly described; complete descriptions are available in the first paper in this series.[1] Calcium oxalate monohydrate, (which will be called calcium oxalate in this paper), is possibly the commonest substance encountered in calculi but does not appear in the form of geometric crystals in ordinary urinary sediments. Occasionally, it occurs as spherulitic growths (wheat sheaves, spirals, rosettes) in the urine of recurrent stone-formers.

Apatite, or calcium phosphate as it will be called, is a complex calcium phosphate, sometimes containing carbonate. There is evidence that the carbon dioxide does not enter into the calcium phosphate structure but is merely physically adsorbed upon crystal interfaces. Apatite is the single crystalline substance usually present when chemical analysis reports calcium phosphate and calcium carbonate. We have not found calcium carbonate present as a separate substance in calculi. Calcium phosphate (or apatite) occurs in combination with one or more substances in the majority of calculi but rarely alone. Of special significance is the fact that it forms the nucleus of the majority of calculi. It is the particular "calcium phosphate" of which bones, teeth and pathological calcifications are composed.

Magnesium ammonium phosphate is commonly called "triple phosphate." The large crystals commonly seen in standing alkaline urines are generally composed of this substance. Together with calcium phosphate it forms most of the large "staghorn" calculi so commonly associated with infection of the urine by urea-splitting organisms.

Uric acid and cystine are described under the next heading.

Several other crystalline substances present in calculi do not appear to be of distinct clinical significance at the present time. Calcium oxalate dihydrate, which composes the common "envelope" crystals seen in standing acid urines, is common in calculi and may have a special significance in stone formation but we do not know what it is. Therefore, the two hydrates of calcium oxalate will be collectively called calcium oxalate in this paper. A second phosphate, calcium hydrogen phosphate, present in 2 per cent of calculi, will also be ignored. A third rare calcium phosphate known as whitlockite[6] has been found in our studies a few times. Urates are rare, contrary to reports in the literature. A urate, sodium acid urate, was found only once.

In the interest of completeness it should be mentioned that several unidentified crystalline substances have been encountered in *small amounts* in a few calculi; further attempts are being made to identify them. Seven urostealiths or waxy calculi have been encountered; they remain unidentified. In addition, a number of supposed "calculi" have been received which resisted all attempts at identification by the usual chemical methods. They were usually offered to physicians as spontaneously passed calculi by patients who were some times malingerers. Such artifacts were generally of mineral origin, commonly terrazzo from the hospital floor, or roadside pebbles. Crystallographic analysis shows them to consist of quartz, feldspar or other rock-forming material usually. These substances, being of mineral origin, are easily identified by the petrographic microscope. A few organic substances such as small seeds, have also been offered as calculi.

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[6] Frondel, C.: Whitlockite: A new calcium phosphate, $Ca_3(PO_4)_2$. Am. Mineral, **26**: 145–152, 1941.

ENVIRONMENT OF CALCIUM-CONTAINING CALCULI

The calcium-containing calculi fall naturally into two groups on a clinical basis. The distinction is based mainly on urinary reaction, although there are some exceptions.

The primary calcium-containing calculi occur in individuals with an acid urine in an apparently normal urinary tract and are usually composed of calcium oxalate or of mixed calcium oxalate and calcium phosphate. If infection is present it is by organisms which do not render the urine alkaline. Occasionally the urine may be neutral or even somewhat alkaline when *examined*. It is important to remember that the reaction of the urine may change on standing. This may explain some of the inconsistencies noted. We have occasionally found that the acid urine from a stone-bearing kidney may be made alkaline when it gets to the bladder by urea-splitting infection limited to the bladder; this may be confusing.

The other group of calcium-containing calculi are generally considered "secondary" calculi,—secondary to or associated with other urinary tract changes, such as obstruction, stasis or chronic infection. The urine is usually alkaline due to the presence of urea-splitting organisms. Magnesium ammonium phosphate enters into the composition of these calculi because of the alkalinity. These stones are generally composed of this substance plus calcium phosphate and are exemplified by the common "staghorn" or dendritic stone.

This classification is summarized in table 1.

It is emphasized that this division on the basis of pH is not always as sharp as table 1 would suggest. Occasionally we have found magnesium ammonium phosphate in the outermost layer of calculi (the layer which was being deposited at the time that the calculus was obtained) from patients whose urine was quite acid. We have also cultured urea-splitting organisms from urine whose pH was 5.5; obviously the organisms were not numerous enough in these cases to have a demonstrable effect on the pH. It seems unnecessary to mention that urine may

TABLE 1. *Conditions of occurrence of calcium-containing calculi*

Content	*Environment*
Calcium oxalate or Calcium oxalate-calcium phosphate	normal urinary tract urine acid usually infection + or −
$MgNH_4PO_4$-calcium phosphate	abnormal urinary tract alkaline urine urea-splitting infection.

be alkaline though uninfected. But marked alkalinity is usually due to urea-splitting infection. Despite these few exceptions the above classification will provide a good working rule of thumb to cover nearly all cases.

It is commonly assumed that all calculi of the "staghorn" or dendritic type are associated with urea-splitting infection; this is not true. About 20 per cent of them are composed of almost pure calcium phosphate and occur in a urine most commonly slightly acid. They usually contain a trace or a few per cent of calcium oxalate but no magnesium ammonium phosphate. These calculi belong in the primary group of stones. Yet they look just like the stones which are associated with urea-splitting infection, being dull grey in color, chalky when dry, and frequently of large size. It may be mentioned that cystine calculi also assume a "staghorn" shape at times.

We commonly divide calcium-containing calculi into "oxalate" and "phosphate" stones, implying that the "phosphate" calculi are secondary stones associated with urea-splitting infection. This is not always true as we have just pointed out. Furthermore, many of the primary "oxalate" stones contain large amounts of phosphate. In fact many of these so-called "oxalate" stones originated as "phosphate" stones because the nucleus is of calcium phosphate. This will be considered later.

As a result of secondary infection by urea-splitting organisms a primary stone of any composition may acquire an external coating of calcium phosphate and magnesium ammonium phosphate and have the external appearance of an "alkaline infection" stone. It is unwise to guess at the composition of a stone from its external appearance. Color is also an unreliable guide. I have seen calcium oxalate, calcium phosphate and uric acid stones all of identical color and texture.

The non-calcium-containing calculi are composed of uric acid or cystine. Usually (but not always) they are "pure" calculi. They occur in an acid urine, usually uninfected (except secondarily).

THE NUCLEUS

A nucleus is that part of a concretion which is formed first and upon which further precipitation from solution occurs to produce growth of the concretion. Crystallographic study has shown that the majority of calculi have a demarcated portion, sometimes of different composition or structure from the rest of the stone, and so situated that it must represent the first portion of the stone formed. Theoretically, this nucleus should be a very minute structure,—the first crystalline particle deposited from solution. In calculi the term may be applied to a larger structure, varying in size from microscopic to a number of millimeters in its dimensions. Obviously, this larger "nucleus" is due to further deposition (from solution) upon the first particle or to aggregation of separate and co-existing particles.

In some calculi no nucleus is discernible. Study of the cross section may reveal such irregularity of structure that no point of origin is suggested. Or the nucleus may have dissolved, especially if it was located upon the external surface of the calculus (as will be mentioned later). Only experience may suffice to determine the sequence of development in a stone of mixed and complex structure.

Blood clot and desquamated epithelium have been mentioned as possible nuclei upon which stones might form. If they were small they would eventually be replaced by calcium phosphate in the process of calcification so that we cannot rule out such substances as possible precursors of some of the calcium phosphate nuclei. However, I have carefully examined a number of renal calculi said to have followed trauma, sometimes associated with hematuria, and have rarely found any evidence suggesting that blood clot had anything to do with formation of the kidney stone. The development of a bladder stone upon a foreign body introduced to the bladder need not be considered here.

Nucleus formation. In general two types of nucleus are found in or on urinary calculi and their formation is explained by existing theories.

1) Randall[3] described a precalculous lesion of unknown nature occurring in the renal pyramid in a subepithelial or interstitial position in relation to the calyx. Some of these lesions, by the accident of their position immediately beneath the epithelium of the pyramid, become exposed upon the surface of the papilla when the overlying epithelium erodes away. In this position they are bathed by the supersaturated urine of the calyx and urinary salts are deposited upon them resulting in growth. Eventually a calculus is formed adherent to the renal papilla and projecting into the calyx; this drops off and becomes a free stone.

This is the type 1 lesion of Randall, the calcium plaque. Our studies have shown that this subepithelial plaque is most commonly composed of calcium phosphate, specifically apatite, but plaques of calcium oxalate monohydrate, uric acid and urates are also encountered. The calcium phosphate plaques may be easily explained as the result of interstitial calcification in a localized area of tissue in the renal papilla in which degeneration or necrosis had occurred. The plaques of other compositions cannot readily be explained on this basis. Uric acid and urates are known to occur in the tissues in other parts of the body but this is not true of calcium oxalate. The most likely explanation is that these salts are extruded to the interstitial (peritubular) tissue as a result of renal tubular breakdown. Randall states that the calcium salt is first deposited as fine granules in the basement membrane of the collecting tubule and that gradually such granules coalesce until the calcification appears as a complete ring encircling the tubule with resulting gradual destruction of the tubule. Randall identified his calcium salts by staining reactions which could not discover the oxalate radicle. Incomplete studies by crystallographic techniques have shown calcium oxalate monohydrate occurring in peritubular position in the renal papilla.

As a result of personal dissection of many kidneys removed at autopsy it has been possible to confirm Randall's observations and to add details. In figure 1, *A* are seen several plaques high upon the slope of the renal papilla in a human kidney just after they had eroded to the calyceal surface and had begun to acquire a deposit of salt from the urine of the calyx. Usually they are much less irregular in shape than is depicted here. In figure 1, *B* are shown two small calcium oxalate calculi formed upon calcium phosphate nuclei in a similar position

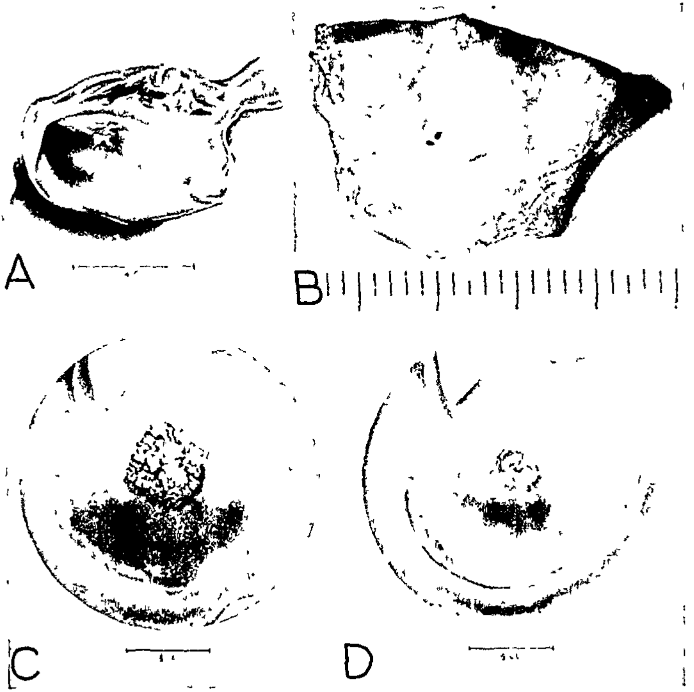

FIG 1. *A*, calcium plaques upon excised renal papilla of human kidney, after erosion of overlying epithelium and exposure of lesion on calyceal surface, with acquired deposition of salts from supersaturated urine of calyx *B*, calcium oxalate calculi formed upon calcium phosphate nuclei originating as in *A*. (Scale in millimeters) *C*, calcium oxalate calculus perched upon apex of human renal papilla *D*, showing ulceration in papilla after stone depicted in *C* was removed.

on the papilla. In figure 1, *C* is shown a somewhat larger calcium oxalate calculus perched upon the summit of the papilla. Actually this stone was found free in the calyx and the tip of the papilla showed the shallow ulceration depicted in figure 1, *D*. The stone could be made to fit the shallow cavity exactly.

Our studies of calculi from clinical sources have shown that many stones, mostly of the calcium oxalate variety, have structures upon their surfaces which can only be explained by assuming that they originated by attachment to a surface. Shallow cup-shaped depressions or concavities occurring on one surface of the stone were often of a shape suggesting that they had capped the renal papilla or had originated upon the slope of the papilla. Furthermore, in the bottoms of some of these concavities there was often a tiny irregular nodule or pedicle, suggesting a point of attachment. These pedicles are composed of calcium phosphate (apatite) or, less commonly, of calcium oxalate monohydrate They represent the nucleus of the stone The stones themselves are usually of calcium

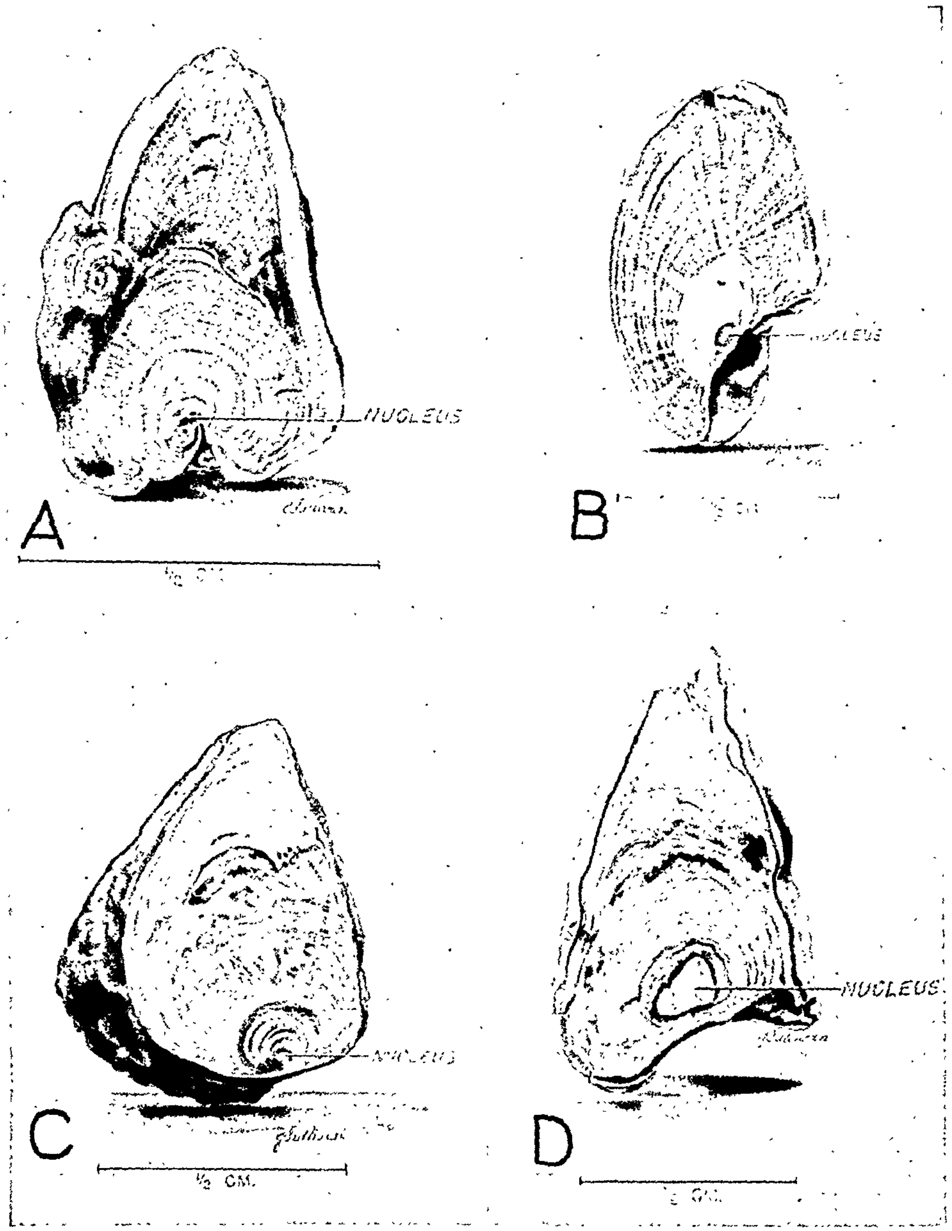

FIG. 2. Calculi which have developed from nuclei occurring as calcium plaques upon surface of renal papilla. Showing asymmetric structure of stone with nucleus upon surface of stone, generally at bottom of a depression or concavity. Concavity lacking in *C*. In *D* nucleus has been covered by minimal deposition from urine after stone has separated from renal papilla.

oxalate or mixed calcium oxalate-calcium phosphate composition. Often the pedicle is missing or shows evidence of partial dissolution, especially when composed of calcium phosphate. As will be discussed later, it is reasonable to assume that dissolution of calcium phosphate nuclei (or pedicles) may occur in a very acid urine. Occasionally there is found a dried bit of membrane still adherent to the concavity of the calculus which undoubtedly represents epithelium torn from

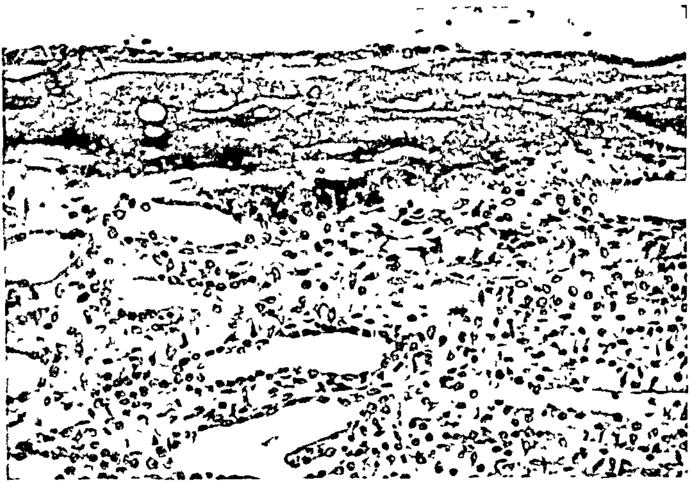

Fig. 3. Subepithelial (precalculous) lesion produced experimentally in renal papilla of rat's kidney by feeding magnesium deficient diet for 2 months. Urine was sterile. Erosion of epithelium of papilla with fibrinoid reaction beneath. Both tubules and interstitial tissue are involved. No leukocytic infiltration. Erosion of epithelium is followed by deposition of a flat plaque of calcium phosphate. Lesion is not upon apex of the papilla but upon the slope. (×300).

the papilla when the stone broke loose. These structures on calculi are depicted in figure 3 in a previous paper in this series.[5]

Calculi which originate in this manner, then, have a nucleus situated upon the external surface of the stone, usually in a depression or concavity (as mentioned above). On cross section they are seen to have an eccentric structure about the nucleus, showing that growth was influenced by the attachment of the nucleus to a surface as in figure 2. Occasionally the nucleus lies a slight distance beneath the surface of the stone and becomes covered by minimal deposition of salts after the stone breaks loose from the renal papilla as in figure 2, *D*.

Following Hammarsten[2] it has been possible to produce a precalculous subepithelial lesion and also stone formation upon the renal papilla in sterile urine in rats by feeding experiments. The calculi are depicted in figure 5 in the previous paper in this series.[5] The diets used were normal maintenance diets except for some magnesium deficiency. Figure 3 represents such a subepithelial lesion in the rat's kidney. We are not sure that it is the exact counterpart of the Randall's plaque lesion in the human but it is similar.

2) The second mode of nucleus formation depends upon the fact that urine is a supersaturated solution of salts. Under conditions of considerably increased supersaturation existing in the kidney tubule, calyx or renal pelvis precipitation of a salt must occur. Centers of crystallization are formed which act as nuclei for further precipitation. This process is known as exsolution in physical chemistry.

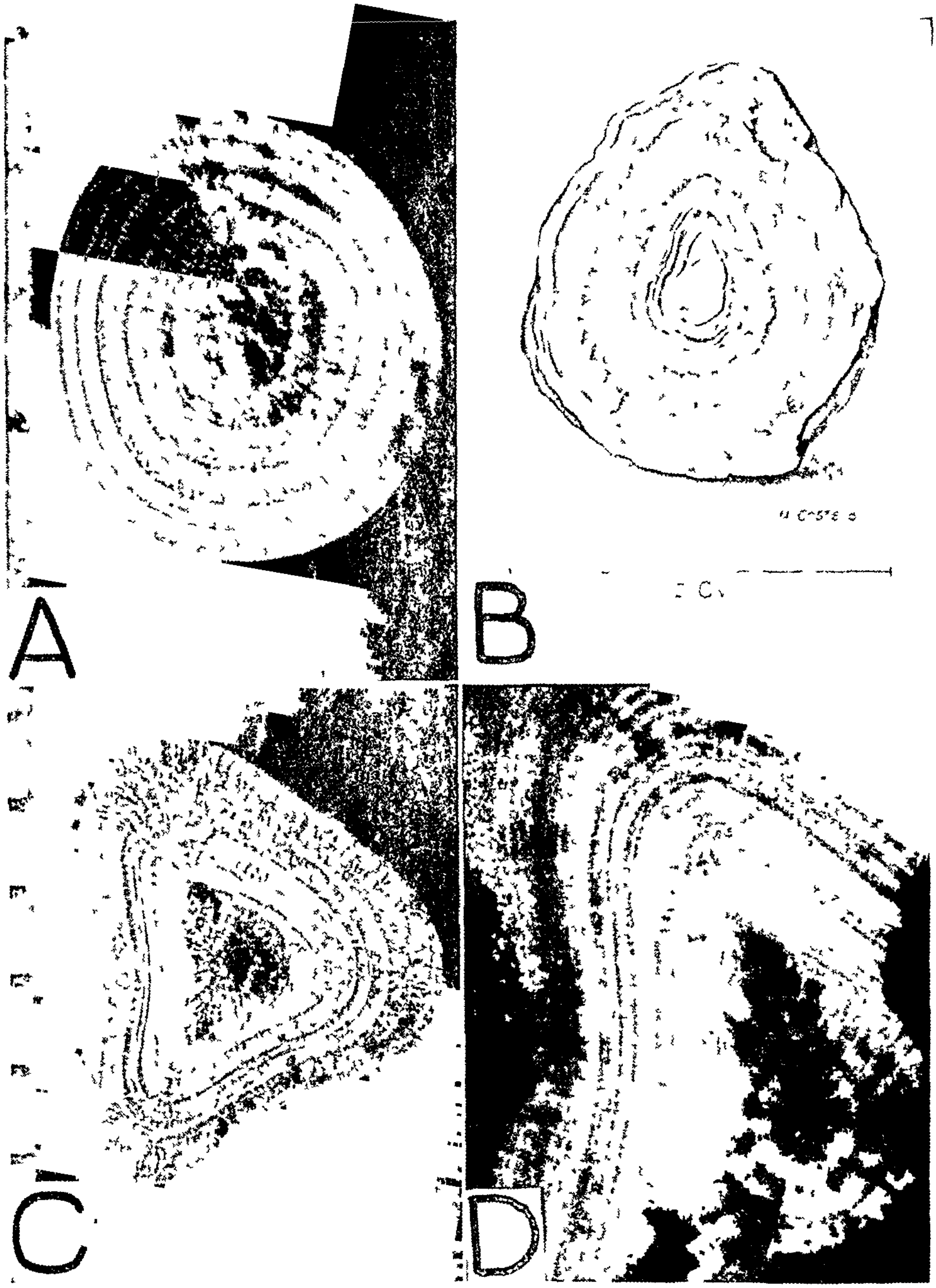

Fig 4. Calculi produced by precipitation of urinary salts upon nucleus in urine itself. Showing central nucleus surrounded by symmetrical concentric layers *A* and *C* are entirely of calcium oxalate, including nucleus *B* is of calcium oxalate with a calcium phosphate nucleus *D* represents left upper portion of *C* (somewhat magnified) Stone has been ground down to thickness of 1/40 mm. so as to render thin section transparent Note perfect symmetry of the central nucleus

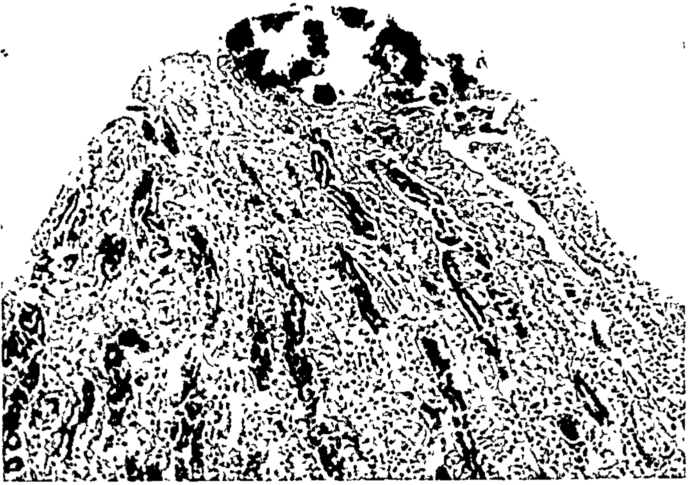

FIG. 5. Cross section of renal papilla of rat showing experimentally produced calcium phosphate calculus upon apex of papilla. Impaction of papillary duct by inspissated urinary salts followed by anemic infarction, necrosis and sloughing of adjacent area with stone formation. Type 2 lesion of Randall. (×150)

This is equivalent to the type 2 lesion of Randall in which intratubular calcification occurs. It is the type of lesion which occurs in the hyper-excretory state and is exemplified by sulfonamide concretions.[7] The formation of sulfonamide concretions is an acute affair so that the crystals merely clump together to form a loose aggregate. In the more slowly-forming urinary calculus the structure is compact.

If precipitation of this type of nucleus occurs in the renal tubule the nucleus is usually ejected into the calyx before further deposition upon it interferes with its passage down the tubule. Stone growth occurs in the calyx or renal pelvis, if, by coincidence, the nucleus should be retained in the kidney. Undoubtedly very many nuclei and tiny calculi in various stages of development are passed to the exterior before they are large enough to produce symptoms in passage.

Calculi formed in this manner may have a central nucleus surrounded by symmetrical concentric laminations as in figure 4. This is because the nucleus is not attached to a surface but is surrounded on all sides by urine. Or there may be no evidence of regular structure at all, especially in "staghorn" or dendritic calculi in which growth may be restricted by the containing cavity, be it calyx or renal pelvis.

If the intratubular growth is very rapid the concretion may become impacted in the distal collecting tubules or papillary ducts as Randall has shown.

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[7] Prien, E. L.: The mechanism of renal complications in sulfonamide therapy. N. Eng. J. Med., 232: 63-68, 1945.

The impaction is accompanied by varying degrees of local anemic infarction and necrosis about the tubules at the apices of the pyramids. Necrosis may be followed by sloughing of the apex of the papilla, exposing the impacted nucleus to the supersaturated urine of the calyx, with subsequent development of a calculus. Such a stone may have a structure approximating that formed from a plaque (type 1 lesion) and may be indistinguishable from it. We have been able to reproduce the picture in experimental urolithiasis in rats without urinary infection, as in figure 5. This shows a cross section of the renal papilla of a rat with a calcium phosphate calculus perched upon the apex of the papilla. This lesion is distinct from the one depicted in figure 3 but both may occur in the same kidney. The process depicted in figure 3 occurs upon the slope of the papilla and may be identical with Randall's type 1 lesion; it has not been carefully studied. The process depicted in figure 5 occurs at the apex of the papilla and appears to be identical with Randall's type 2 lesion.

What is the evidence for nucleus formation by direct precipitation from the urine? Figure 4, *A* depicts a spherical calculus with a centrally placed nucleus of calcium oxalate surrounded by symmetrical concentric layers of the same substance. The calculus in figure 4, *B* is similar but has a calcium phosphate nucleus. Figure 4, *C* shows a symmetrical pyramidal stone with a central nucleus; when ground down to a $\frac{1}{40}$ mm. in thickness to render it transparent the thin section (fig. 4, *D*) shows the perfect symmetry of the nucleus. In figure 10,*3* and figure 15,*2*, in the first paper of this series[4] are shown pure calcium phosphate and uric acid calculi respectively with central nuclei surrounded by symmetrical concentric layers, also suggesting an origin *other* than from a surface, and readily explained by precipitation of salts from the urine itself.

Figure 8,*1* in the aforementioned paper[4] shows a calcium oxalate calculus composed of many nodules which have coalesced. In the center of each nodule is a nucleus. It is difficult to understand how this stone could have originated from a plaque upon a mucosal surface unless each nodule arose from a separate plaque. The number of plaques in a single kidney has not exceeded 10 in my experience; the number of nodules in some of these calculi exceeds 100. Furthermore, examination of every nucleus in such a calculus shows that they are all perfectly symmetrical structures. It seems probable that such calculi are formed from multiple nuclei which originate by precipitation from the urine of the renal calyx or pelvis. Each nucleus develops into a nodule. The nodules then coalesce to form the stone.

Most of the "staghorn" calculi of alkaline infection originate by direct precipitation from the urine itself rather than as mural (Randall's) plaques. They may have a definite central nucleus or merely a central zone of calcium phosphate, composed of a structureless mass of aggregated crystals, sometimes several cm. in diameter as in figure 11 in the first paper in this series.[4] Many calcium oxalate, most uric acid and all cystine calculi apparently originate by direct precipitation from the urine. It is not necessary to assume that a nucleus is always formed first and that other crystalline particles precipitate directly upon this nucleus from the urine. The structure of some calculi suggests that they are composed of crystals which precipitated independently of each other and only secondarily became aggregated or clumped together to form the stone. This is especially true of cystine calculi.

From the evidence presented it seems reasonable to believe that urinary calculi originate in two ways:—1) from nuclei originating beneath the epithelium of the renal papilla, and 2) from nuclei crystallizing from the urine itself.

Composition of nuclei. The majority of the nuclei of calcium oxalate and of mixed calcium oxalate-calcium phosphate calculi are composed of calcium phosphate; the remainder are of calcium oxalate. This finding may have considerable clinical significance as will be mentioned later.

The nuclei of "pure" calcium phosphate calculi are composed of the same substance, sometimes with a little calcium oxalate. The nuclei of mixed calcium phosphate-magnesium ammonium phosphate calculi are composed of calcium phosphate or of calcium phosphate plus magnesium ammonium phosphate. When calcium phosphate is precipitated *without* magnesium ammonium phosphate we infer that this happened in a slightly acid or neutral urine. When calcium phosphate is accompanied by magnesium ammonium phosphate we infer that the urine was alkaline since the latter substance usually precipitates only in alkaline urine. Almost invariably this is found to be due to urea-splitting infection. Therefore, when only calcium phosphate is found in the nucleus of a calculus of mixed calcium phosphate-magnesium ammonium phosphate composition it is reasonable to assume that urea-splitting infection *followed* the formation of the nucleus. If magnesium ammonium phosphate occurs in the nucleus it is reasonable to infer that urea-splitting infection *preceded* the formation of the nucleus.

The nuclei of uric acid and cystine calculi are usually composed of those same substances.

Statistically, calcium phosphate composes the nucleus of the majority of calculi. In the preceding paper in this series,[5] written some 5 years ago, it was stated that the majority of stone nuclei did not contain calcium phosphate, or apatite as it was called. At that time only a casual study of nuclei had been made. The previous statement is herewith retracted.

Nonspecificity of the nucleus. Despite what has been said above it is believed that the nucleus, particularly of calcium-containing calculi, is nonspecific and does not govern the kind of substance precipitated upon it. The substance precipitated will depend upon the urinary pH and the degree of supersaturation of the urine by various stone-forming crystalloids at the time. In general the evidence suggests that the same calcium phosphate nucleus may develop into either a calcium oxalate stone if the urine remains acid or into the typical alkaline-infection "staghorn" stone if urea-splitting infection should follow.

INFLUENCE OF PH ON COMPOSITION OF CALCULI

The composition of the stone which is formed will depend upon the urinary pH to a large extent. Failure to recognize this explains some of our failures to prevent recurrence. Meyer[1] has made extensive studies of urinary saturation by dissolved stone-forming substances; I have found it helpful to construct a diagram from his values. Meyer determined the average amount of each of the stone-forming salts present in a series of normal urines from which there had been no previous precipitation. Then he calculated how much this average amount of each salt would saturate the urine at various pH levels at body temperature. (It is, of course, strictly incorrect to speak of the amount of stone-forming substances dissolved in urine because they do not exist as such but only as dissociated ions.) In making his calculations, which are quite complicated, Meyer assumed that urine is a simple aqueous solution of the various crystalloids and he took into his calculations the increase in solubility resulting from the presence of the ions of other salts in the urine. He concluded that he could satisfactorily explain the capacity of the urine to hold in solution the large amounts of relatively insoluble salts without recourse to colloids. While his work has been criticized by the proponents of the colloid theory there has been found a striking degree of

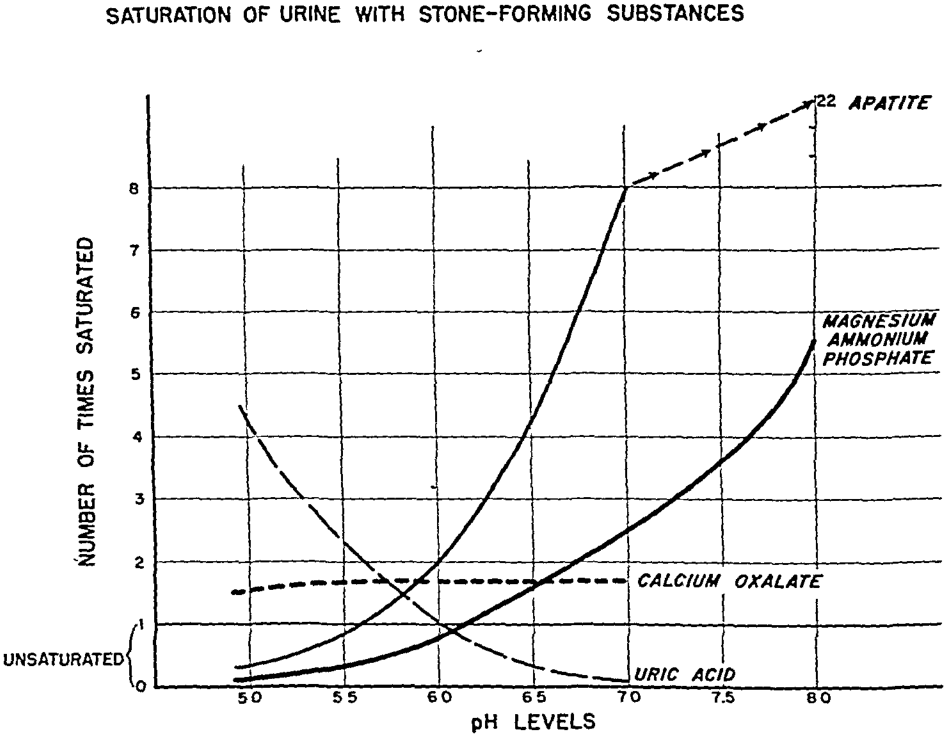

FIG. 6. Saturation of urine by stone-forming salts. Average amount of each salt present in a series of normal urines was determined. Aqueous solubility of this average amount of each salt in terms of the urinary saturation at each pH level was then determined, taking into account reciprocal effects on solubility of other ions in solution. (After Mayer.)

Increasing supersaturation means increasing insolubility of salt. Thus, saturation of calcium phosphate (apatite in diagram) doubles for each half unit increase in pH between 5.6 and 7.0. In other words, insolubility doubles with each half unit increase in alkalinity. Or, conversely stated, lowering of the pH one half unit (as by acidification therapy) doubles the solubility.

Solubility changes for magnesium ammonium phosphate are similar to those for calcium phosphate but less marked. Change of pH has practically no effect on solubility of calcium oxalate. Curve for uric acid shows increase in solubility (decrease in saturation) with increasing alkalinity.

correlation between the kind and degree of precipitations predicted by his calculations for the major constituents and their actual composition as determined in the present study.

Meyer has stated that normal urine is commonly supersaturated to the extent of 2 to 4 times its normal aqueous solubility with one or more of the common stone-forming salts at all pH levels, and that this degree of supersaturation may continue to exist for a time, (probably hours), without precipitation occurring. By this is meant that there is in solution in urine 2 to 4 times as much of a stone-forming salt as could be dissolved in an equal amount of water. (The amount of a salt which just dissolves in water at a certain temperature produces a just saturated solution or a saturation of 1. If twice this amount of salt is dissolved in this volume of water the saturation is 2, etc.) Referring to figure 6 it will be seen that curves have been constructed to show the degree of saturation of the urine by the various urinary salts at different pH levels. After determining the average amount of each salt present in a series of normal urines, Meyer calculated how much this average amount of salt would saturate the urine at various pH levels, *if it could be held in solution at all pH levels,*—which is impossible. For instance, in the case of calcium phosphate, (apatite in the diagram), the average amount present in normal urine would saturate it 22 times at pH 8.0. Actually, some of this salt would precipitate from solution long before this pH level was reached.

A casual inspection of figure 6 might suggest that the curves show the solubility of the various salts in urine at different pH levels,—how much of a certain salt may be dissolved in urine at a certain pH. Thus, at first glance it might appear, for example, that calcium phosphate (apatite) was more soluble as the pH rose. Actually, the curve shows the insolubility (expressed as degree of supersaturation) of calcium phosphate at the alkaline levels. Starting at pH 5.6 the degree of supersaturation doubles (approximately) with each 0.5 unit rise in pH. Normal urine is usually unsaturated with this salt below pH 5.6, twice saturated at pH 6.0, 4 times supersaturated at pH 6.5 and 8 times supersaturated at pH 7.0. Another way of expressing the same idea is to say that the average amount of calcium phosphate present in normal urine is only half as soluble at pH 6.0 as it is at pH 5.6, ¼ as soluble at pH 6.5 and only ⅛ as soluble at pH 7.0 as it is at pH 5.6.

At the time that Meyer did his work the commonest calcium phosphate present in calculi was considered to have the formula $Ca_3(PO_4)_2$; later studies have shown that this substance has a much more complex structure and is known as apatite. In a private communication to the writer Meyer has stated that his values may be applied to apatite.

Magnesium ammonium phosphate is also very insoluble in alkaline urine. Normal urine is unsaturated with this substance below pH 6.2 and about 2.5 times supersaturated at pH 7.0.

Referring to the curve for uric acid it will be seen that the average amount of uric acid present in normal urine supersaturates it 4 times at pH 5.0 but unsaturates it above pH 6.0. As the urine becomes more alkaline the solubility of uric acid increases. This is the basis of treatment for the prevention of recurrent uric acid stone,—alkalinization of the urine to render uric acid more soluble.

Cystine is not shown because it is not present in appreciable amounts in normal urine. In the patient with cystinuria the curve would be somewhat similar to that for uric acid,—and the treatment the same.

In the case of calcium oxalate a slight degree of supersaturation, 1.7 times, is almost constant, regardless of pH. The curve shows the futility of trying to control calcium oxalate deposition by altering the pH,—the solubility remains practically unchanged.

In a diagram such as figure 6 the precise values are unimportant and an approximation will suffice. What is important, however, is the trend taken by the various curves under the influence of changing pH, suggesting what must be done to decrease the insolubility (or the degree of supersaturation) of the various salts. For example, it may be pointed out that a decrease in the urinary pH from 7.0 to 6.5 doubles the solubility of the average amount of calcium phosphate normally present in urine,—from 8 times supersaturation to 4 times supersaturation. A decrease in pH from 7.0 to 6.0 quadruples the solubility,—from 8 times supersaturation to 2 times supersaturation. This suggests the value of even small changes in pH produced by acidification therapy in those parts of the pH range where the curves are steep. It should be remembered, however, that hypercalcinuria may be present in the stone-forming individual so that a half unit decrease in pH will not double the solubility of the larger amount of calcium phosphate present in the urines of patients with hypercalcinuria,—but it would produce some increase in solubility.

With the onset of urea-splitting infection marked alkalinity of the urine occurs and magnesium ammonium phosphate and calcium phosphate are precipitated. The common "staghorn" calculus of alkaline infection is composed of these substances. Figure 6 demonstrates the excessive insolubility of these substances in alkaline urine and emphasizes the necessity of diminishing this alkalinity if we are to prevent recurrence (or growth) of such calculi. This means eradication of urea-splitting infection which is often a difficult problem, even in these days of potent antibiotics. If the pH cannot be lowered recurrence (or growth) of stone will usually follow. In severe unilateral calculous pyonephrosis complicated by urea-splitting infection the surgeon should consider carefully before deciding to save a considerably destroyed and largely functionless kidney in the presence of a good contralateral kidney. Blind adherence to the dictum of conservation of kidney tissue is not always wise, particularly when there is not much kidney tissue to save, when stone recurrence is inevitable and the risk of serious infection of the other kidney is increased.

One further point: supersaturated solutions may maintain their salts in solution *for a limited time.* If this time period is exceeded precipitation occurs. Similarly, urine may maintain its salts in solution *for a time.* If this time period is exceeded because of urinary stasis precipitation occurs. Clinically, this is observed when ureteropelvic obstruction results in formation of stone in an uninfected hydronephrotic kidney. So that in addition to degree of supersaturation of urine we have the length of time during which this supersaturated state exists as a factor in stone formation.

Significance of the nucleus. A supersaturated solution may remain unchanged for a variable length of time without precipitation occurring if no nuclei are added to the solution. If a nucleus (of the same substance or other substance) is added to a supersaturated solution precipitation will occur more rapidly; in fact, mass precipitation may occur. This is known in physical chemistry as "seeding" the solution. With a nucleus present it may be impossible to supersaturate a solution; precipitation may occur whenever the saturation point is exceeded.

In the same way the presence of a nucleus in the urinary tract may reduce the ability of the urine to hold salts in supersaturated solution, whether in the normal or stone-forming individual. If a nucleus (or stone) is present in the efferent channels precipitation may occur whenever the saturation point is exceeded. However, if *no* nucleus is present in the urine it may be able to hold in solution 2 to 4 times as much stone-forming salt as can be held with a nucleus present. (Presumably the ever present desquamated epithelial cells do not act as nuclei.) It would seem desirable, therefore, to conserve, if possible, this capacity of urine to hold its salts in supersaturated solution by preventing nuclei from forming.

The most obvious principle underlying a stone management program is the prevention of marked urinary supersaturation. If we are permitted to theorize a bit it would seem that those nuclei which originate in the urine as a result of the supersaturated state (hyperexcretory or exsolution type) might form in a very short time in markedly concentrated urine in stone-forming individuals. Therefore, even transient periods of oliguria are contra-indicated in such individuals (but not in normal individuals). They should keep up their fluid intake more or less around the clock. On the other hand, nuclei which originate from Randall's plaques would not be prevented by keeping the concentration of the urinary crystalloids at a low value because they do not originate from supersaturated urine but from the tissue of the papilla. However, growth of calculi upon such exposed plaques, and upon all nuclei, would be retarded if the urine were kept dilute.

Calculi of predominant calcium oxalate composition occur in at least two thirds of our stone cases in North America. It is generally stated that there is little that can be done to prevent such calculi from forming except to decrease urinary supersaturation by forcing fluids. This is not necessarily true. Since the majority of such calculi have nuclei of calcium phosphate, since calcium phosphate is increasingly soluble in an acid urine, and since the absence of a nucleus may permit the urine to maintain its dissolved calcium oxalate in a somewhat supersaturated solution more readily, (instead of precipitating it upon the nucleus whenever the saturation point is exceeded), it is suggested that we try to prevent calcium oxalate stone formation by preventing calcium phosphate nuclei from forming thru acidification therapy. This will be considered at length in a later clinical paper.

In this consideration of the physical chemistry of stone formation we have probably been guilty of over-simplification, and even of speculation. Precipitation uric acid increases. This is the basis of treatment for the prevention of recurrent uric acid stone,—alkalinization of the urine to render uric acid more soluble.

Cystine is not shown because it is not present in appreciable amounts in normal urine. In the patient with cystinuria the curve would be somewhat similar to that for uric acid,—and the treatment the same.

In the case of calcium oxalate a slight degree of supersaturation, 1.7 times, is almost constant, regardless of pH. The curve shows the futility of trying to control calcium oxalate deposition by altering the pH,—the solubility remains practically unchanged.

In a diagram such as figure 6 the precise values are unimportant and an approximation will suffice. What is important, however, is the trend taken by the various curves under the influence of changing pH, suggesting what must be done to decrease the insolubility (or the degree of supersaturation) of the various salts. For example, it may be pointed out that a decrease in the urinary pH from 7.0 to 6.5 doubles the solubility of the average amount of calcium phosphate normally present in urine,—from 8 times supersaturation to 4 times supersaturation. A decrease in pH from 7.0 to 6.0 quadruples the solubility,—from 8 times supersaturation to 2 times supersaturation. This suggests the value of even small changes in pH produced by acidification therapy in those parts of the pH range where the curves are steep. It should be remembered, however, that hypercalcinuria may be present in the stone-forming individual so that a half unit decrease in pH will not double the solubility of the larger amount of calcium phosphate present in the urine of patients with hypercalcinuria,—but it would produce some increase in solubility.

With the onset of urea-splitting infection marked alkalinity of the urine occurs and magnesium ammonium phosphate and calcium phosphate are precipitated. The common "staghorn" calculus of alkaline infection is composed of these substances. Figure 6 demonstrates the excessive insolubility of these substances in alkaline urine and emphasizes the necessity of diminishing this alkalinity if we are to prevent recurrence (or growth) of such calculi. This means eradication of urea-splitting infection which is often a difficult problem, even in these days of potent antibiotics. If the pH cannot be lowered recurrence (or growth) of stone will usually follow. In severe unilateral calculous pyonephrosis complicated by urea-splitting infection the surgeon should consider carefully before deciding to save a considerably destroyed and largely functionless kidney in the presence of a good contralateral kidney. Blind adherence to the dictum of conservation of kidney tissue is not always wise, particularly when there is not much kidney tissue to save, when stone recurrence is inevitable and the risk of serious infection of the other kidney is increased.

One further point: supersaturated solutions may maintain their salts in solution *for a limited time*. If this time period is exceeded precipitation occurs. Similarly, urine may maintain its salts in solution *for a time*. If this time period is exceeded because of urinary stasis precipitation occurs. Clinically, this is observed when ureteropelvic obstruction results in formation of stone in an uninfected hydronephrotic kidney. So that in addition to degree of supersaturation of urine organisms in all layers of the calculi by appropriate studies. One gathers from a perusal of his paper that he infers some special direct causal relationship between the staphylococci and the stones. The writer believes that a relationship does exist but it is an indirect one, acting through the effect upon urinary pH.

It has been suggested that bacterial infection may influence stone formation by alteration of existing urinary colloids or through introduction of a foreign colloid in an inflammatory exudate. These possibilities are too intangible to evaluate.

EFFECT OF HYPEREXCRETION ON STONE FORMATION

Hyperexcretion of common stone-forming salts into the urine is an important factor in calculus formation. Albright[10] and Flocks[11] have found that many patients with calcium-containing calculi have an increased calcium excretion. The causes of hyperexcretion will be discussed in a later clinical paper.

RESORPTION OF CALCULI

It is possible for small calculi composed of calcium phosphate, uric acid or cystine to be partially or completely resorbed if the urine be kept unsaturated with the salt composing the stone. Optical study of calculi shows evidence of spontaneous resorption at times but it is rarely prominent. The substance which dissolves most readily is calcium phosphate. It has been previously mentioned that calcium phosphate nuclei situated upon the external surfaces of some calculi have shown evidence of resorption. Occasionally they are completely missing. Normal urine is unsaturated with this salt below pH 5.6 (see fig. 6). It seems obvious that a lowering of the pH below this value might cause dissolution of such small externally placed calcium phosphate nuclei. Furthermore, cavities are frequently found in the interior of calculi still partially lined with calcium phosphate. Just how small masses of calcium phosphate deeply situated in the interior may be dissolved through the dense outer layers of a stone remains unexplained but it obviously occurs. The significant solubility of calcium phosphate in very acid urine suggests that acidification therapy may be of value in prevention of calculi having phosphatic nuclei.

THE IMPORTANCE OF VITAMINS AND NUTRITION

It is felt by some that vitamin A deficiency is an important factor in stone formation. Rats were used to demonstrate that avitaminosis causes stone. However, Hammarsten produced calculi in rats on diets completely adequate in regard to all the vitamins and we have been able to reproduce her results. The diets used were stock maintenance diets with adequate vitamins but with a moderate deficiency in magnesium content. If vitamin A was withdrawn the incidence of stone was increased in the rats. The experimental evidence on vitamin A deficiency as a factor in stone formation is conflicting and will not be reviewed here.

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[10] Albright, F. and Reifenstein, E. C.: The Parathyroid Glands and Metabolic Bone Disease. Baltimore: Williams & Wilkins Co., 1948.

[11] Flocks, R. H.: The role of calcium metabolism in the pathogenesis and treatment of calcium urolithiasis. J. Urol., 43: 214–233, 1940.

While avitaminosis and malnutrition probably are factors in the endemic stone areas of Asia it is doubtful that they are factors in most of North America with its high standards of nutrition. I find no reason to give supplementary vitamins to stone-forming individuals who are eating a well-rounded diet.

It is known that a geographical "stone belt" exists in the southeastern part of the United States extending roughly from the eastern part of Virginia, through the Carolinas, western Florida and portions of the states bordering on the Gulf of Mexico. In certain sections this belt of increased stone incidence is said to be rather sharply demarcated from adjacent areas where the stone incidence is not increased—or is normal. It would seem that if a single causative factor is responsible for the increased frequency of stone in this rather extensive area that it must be sought in the soil or water.

In publication No. 664, "Factors Affecting the Nutritive Value of Foods," United States Department of Agriculture, is a map (fig. 4, p. 6) depicting mineral deficiencies of soils. The map shows that the soil is deficient in magnesium in a belt extending from Virginia to Louisiana. This magnesium deficient soil belt approximates the "stone belts" in extent. This may be mere coincidence. However, the possibility that magnesium deficiency may be the factor responsible for the increased stone incidence in this area receives support from Hammarsten's experimental proof that magnesium deficiency causes stone in rats. Here is an opportunity for an interesting study in the etiology of stone here in America.

UNKNOWN FACTORS IN STONE FORMATION

Some of the more tangible aspects of the stone-forming process have been discussed in the preceding paragraphs. The process is one of crystallization from a complex aqueous supersaturated solution. An attempt has been made to explain it as simply as possible in terms of physical chemistry. However, it seems obvious that a hypothesis which seeks to explain stone formation solely on the basis of the foregoing simply physical concepts is inadequate. These same conditions of crystalloid concentration and of pH which appear to produce calculi in one individual must exist at times in others who do not make stone. For example, marked supersaturation of the urine is very common in many men who undergo severe physical exertion and dehydration in hot weather and yet make no stones; the wonder is that stone formation is not more frequent under such conditions. Yet we know that dehydration is an important factor in urolithiasis because of the increased incidence of stone in individuals who move to tropical regions. We also know that hypercalcinuria is a factor in stone formation. However, patients with noninfective phosphaturia are notoriously free from stone despite the fact that their urines are markedly supersaturated with calcium phosphate. In phosphaturia the urine is turbid and alkaline and tends to form sediments; in hypercalcinuria there is not necessarily any turbidity and the urine may be acid but there is a tendency to form stone.

The experimental evidence is also conflicting. Hammarsten found that a relative deficiency of magnesium in the diet of her rats resulted in calcium oxalate or calcium phosphate stones in acid uninfected urine. If urea-splitting infection occurred in such rats on a low magnesium diet there was no evidence of magnesium deficiency in the rat because magnesium ammonium phosphate was precipitated in abundance in alkaline urine—even when a lack of magnesium in the diet of the same animal was the principal cause of stone in acid urine. This is a bit confusing.

Recently Butt[12] has attempted to show that a deficiency of colloidal particles exists in the urines of stone-forming individuals as determined by dark-field microscopy. We have failed to substantiate this study. The subcutaneous injection of hyaluronidase proposed by Butt[13] to enhance the excretion of protective colloids in the urine—and thus to prevent stone,—apparently has not been productive of successful clinical result in the great majority of cases. It has occasionally accelerated stone formation.[14]

No extensive studies have been made of the matrix of calculi or of the precursors of the matrix substance. Boyce and associates[15] found an increase in the urinary mucoprotein of patients with calculous disease. Baker and associates[16] found experimentally that some alteration in the connective tissue ground substance of the *renal papilla is necessary for calcification; herein may lie the secret* of the pathogenesis of the precalculous (Randall's plaque) lesion. Unfortunately the investigation of the noncrystalline components of calculi is beset with greater difficulties than are encountered in the study of the crystalline elements.

DISCUSSION

It would appear that many of the phenomena associated with the stone-forming process may be rather simply explained in terms of physical chemistry. Meyer's[1] fundamental work determined the pH levels at which the various stone-forming salts might precipitate to form stone. With the petrographic (polarizing) microscope it became possible to identify these substances in situ in the calculus and to study the manner in which they are deposited to form the structure of the stone.

Stone structure and composition were correlated with the clinical history and laboratory findings in a number of patients who were closely followed for sometime before consenting to operative removal of their stone. Frequent urinalysis with pH determinations, cultures and x-ray films at intervals, together with a study of the crosssection of the stone, made it possible to reconstruct the deposition of the various layers in terms of pH. When significant alteration of the urinary pH was achieved by treatment it governed the stone-forming salt which was precipitated upon the growing calculus at the time. It should be stated that such fortunate studies were all too infrequently possible; usually neither the clinical course nor the composition of the stone showed the abrupt changes necessary to permit of a close correlation being set up. Several cases in which such correlations were made are described in the last previous paper in this series.[5] As a result of this study it has been possible to delineate more accurately the conditions of occurrence of the calcium-containing calculi.

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[12] Butt, A. J.: Role of protective urinary colloids in prevention of renal lithiasis. J. Urol., **67**: 450–459, 1952.

[13] Butt, A. J., Hauser, E. A. and Seifter, J.: Effect of hyaluronidase on urine and its possible significance in renal lithiasis. J.A.M.A., **150**: 1096–1098, 1952.

[14] Prien, E. L.: Use of hyaluronidase to prevent urinary calculi. Report of a case in which stone recurrence was facilitated by hyaluronidase therapy. J.A.M.A., **154**: 744–747, 1954.

[15] Boyce, W. H., Garvey, F. K. and Norfleet, C. M.: Ion-binding properties of electrophoretically *homogeneous mucoproteins of urine in normal subjects and in patients* with renal calculus disease. J. Urol., **72**; 1019–1031, 1954.

[16] Baker, R., Reaven, G. and Sawyer, J.: Ground substance and calcification: the influence of dye binding on experimental nephrocalcinosis. J. Urol., **71**: 511–522, 1954.

That calcium phosphate comprises the nucleus of the majority of stones of calcium oxalate composition may possibly be the most important finding reported here. It is probable that it is present in the nucleus of the *great* majority of such calculi; but such a statement must depend upon a numerical study. This will be done when time permits.

The marked increase in solubility of calcium phosphate with increasing acidity of the urine has been described. According to the diagram (fig. 6) a change in pH from 7.0 to 5.6 (as by acidification therapy) will increase the solubility of the average amount of calcium phosphate present in normal urine 8 times. It will be objected that the increase in solubility of calcium phosphate in the hypercalcinuric urine of most recurrent stone-formers will be less than the above figure, which is true. However, there will be a significant increase in solubility even in these cases. The writer finds the idea of acidification of urine to prevent calcium phosphate nuclei especially attactive in one particular group of cases. During hot weather there are many individuals who have small calcium oxalate calculi, often recurrent. These are the common ureteral stones, usually passed spontaneously or by the aid of cystoscopic manipulation. In this group of cases the urine is usually acid and there is frequently no demonstrable hypercalcinuria. A goodly percentage of such calculi have calcium phosphate nuclei. Why not use acidification therapy to increase the acidity of the urine in recurrent stone-formers of this type during the season when such stones are prevalent?

The total significance of the nucleus of the calculus is unknown. Probably the recognition of the nucleus is unimportant in a calculus composed of the same substance throughout. But when the nucleus is of different composition than the remainder of the stone it may be important to know this as in the following case. A recurrent stone-former was thought to have hyperparathyroidism on the basis of predominant calcium and phosphorus in his calculi as determined by chemical analysis and the finding of a somewhat elevated blood serum calcium level. Subsequently several of his calculi were made available for crystallographic study. A tiny nucleus of uric acid was found in the center of each stone; this had been missed by chemical analysis. While the finding of a uric acid nucleus does not rule out the possibility of hyperparathyroidism it conclusively proved in this case that that disease was not the primary cause of recurrent stone.

Even if all the compounds in a calculus are related, (as calcium oxalate, calcium phosphate and magnesium ammonium phosphate are related in the calcium stone series), it may be important to know where in the stone the various substances are located. It may be loosely stated that there are but two fundamental mechanisms producing the supersaturation responsible for the formation of recurrent calcium stone,—too much calcium salt getting into the efferent urinary channels (hypercalcinuria) and too great insolubility of phosphate salts in the urine due to excessive alkalinity, usually of urea-splitting infection. (An apparent exception is provided by the common small calcium oxalate stone seen in many individuals, especially in hot weather. We have not found either of these mechanisms to be present in these cases. Possibly extreme but transient supersaturation may be a *factor.*) *Hypercalcinuria may result in precipitation of calcium phosphate* or of calcium phosphate plus calcium oxalate; urea-splitting infection results in precipitation of calcium phosphate plus magnesium ammonium phosphate. In a program for prevention of recurrence of stone it becomes important to know which mechanism is primarily responsible for stone formation. As has been stated, if magnesium ammonium phosphate is present in the nucleus or center of a stone it is very probable that urea-splitting infection was responsible for stone formation; if this substance is absent in the nucleus but present in the outer layers it is probable that hypercalcinuria was primarily responsible and that urea-splitting infection supervened as a complication of stone growth. For *example, the removal of parathyroid glands in a patient who was hyperpara*thyroidism, recurrent calculi, and urea-splitting urinary infection will not necessarily result in cessation of stone recurrence; the urea-splitting infection should also be eradicated to accomplish this. The converse is probably also true; eradication of urea-splitting infection in a patient whose calculi have magnesium ammonium phosphate deposited only in the outer layers will not necessarily stop his stone formation. So that it may be of clinical importance to know where in the stone the various salts are located.

As an example of the inadequacy of many chemical analyses of calculi the following may be cited: The writer was asked what conclusion might be drawn from a report of uric acid and ammonia in a calculus. No further information was available. A fairly logical reconstruction of the actual composition of the stone would seem to be as follows: The presence of ammonia in a calculus almost certainly means that it occurred as magnesium ammonium phosphate and that urea-splitting infection was probably present in the urine. In a series of some 6000 calculi we have rarely found magnesium ammonium phosphate present in the center of a calculus and absent in the outer portion. This must mean, of course, *that if urea-splitting infection and a calculus co-exist that the infection* is not eradicated while the stone remains in the urinary tract. (Obviously the outermost layer of the calculus represents the condition present at the time that the stone was removed.) The reverse situation in which magnesium ammonium phosphate occurs solely in the outer layers of a stone is very common and has been discussed early in this paper. The finding of uric acid and ammonia in a calculus must mean, then, that the nucleus or the central portion of the calculus must have been composed of uric acid and that urea-splitting infection supervened. In the resulting alkaline urine no more uric acid was precipitated because this substance is quite soluble above pH 6.0. It may be confidently stated that calcium phosphate must have occurred in this stone along with uric acid and ammonia. Only extremely rarely (twice in 6000 calculi), have we found magnesium ammonium phosphate without calcium phosphate accompanying it.

These examples serve to illustrate that information of clinical value may be obtained from the careful analysis of all parts of a calculus. The time-honored custom of presenting the removed calculus to the patient may please him at the moment but may not be in his best interest, having in mind that recurrence occurs in a significant percentage of cases. Probably the surgeon who returns the stone to its owner should not be criticized in view of the well-known inadequacy of medical management programs to prevent recurrence of stone.

The author would like to hazard the prediction that effective regimens to prevent recurrence may be found. Flocks[11] found a high urinary calcium excretion in approximately 66 per cent of patients with calcium-containing calculi and in all cases with recurrent or rapidly growing stones. At the present time it does not seem highly probable that we will learn all the various causes of hypercalcinuria or how to correct them. While we quickly think of hyperparathyroidism as a cause for increased urinary calcium excretion which may be corrected (by surgery), it must be realized that the great majority of cases of hypercalcinuria are due to unknown causes. If we are to prevent stone recurrence in these cases it will be necessary to decrease the marked supersaturation of the urine by stone-forming crystalloids. Forcing of fluids to dilute the urine is the most obvious and most reliable method but its limitations are obvious, it is inconvenient and it has failed, either when used alone or in conjunction with other methods, to accomplish the desired result. For patients with calcium-containing stone a decrease in dietary calcium is of some value, especially in those patients who are consuming a high calcium diet. But there are many patients who continue to have hypercalcinuria and to make stones even when on a low calcium diet—and without having a urea-splitting urinary infection. This will not be considered further here because this is a non-clinical paper. If we are to be completely successful in preventing stone recurrence it will probably be necessary to block the absorption of calcium from the gastro-intestinal tract or to stabilize the solubility of the stone-forming crystalloids in the urine itself. The first is probably undesirable on a long term basis because it would interfere with normal homeostatic mechanisms. Under stabilization of solubility we may include acidification therapy for calcium-containing calculi and alkalinization for uric acid and cystine calculi, and any other mechanisms, including the colloidal, by which a substance excreted into the urine may enhance or stabilize the solubility of the stone-forming crystalloids. Having in mind the disinclination of patients to co-operate fully on a program which is inconvenient it would seem that such therapy should be orally administered.

In the present paper an attempt has been made to elucidate some of the phenomena of the stone-forming process in terms of physical chemistry. It is probable that other unknown factors exist. It seems reasonable to hope that the application of therapeutic methods based on physicochemical principles may ultimately enable us to prevent stone in the individual predisposed to recurrence.

SUMMARY AND CONCLUSIONS

An intimate study of the structure and composition of some 6000 human urinary calculi has been made by crystallographic techniques and correlated with the clinical case history in selected cases. As a result of this study it seems pertinent to consider some principles of physical chemistry which bear upon calculus formation and prevention, with particular emphasis on the nucleus and the factors governing urinary saturation with the stone-forming salts.

From the clinical standpoint there are apparently only three important crystalline substances in calcium-containing calculi, calcium oxalate, calcium phosphate (apatite), and magnesium ammonium phosphate. Uric acid and cystine are also important.

The calcium-containing calculi fall naturally into two groups on a clinical basis, mainly on the basis of urinary reaction. There are a few exceptions. The primary calcium-containing calculi occur in individuals with an acid urine in an apparently normal urinary tract and are usually composed of calcium oxalate or of mixed calcium oxalate and calcium phosphate. If infection is present it is by organisms which do not render the urine alkaline. The secondary calcium-containing calculi are usually associated with other urinary tract processes and the urine is usually alkaline due to urea-splitting infection. They are usually composed of calcium phosphate and magnesium ammonium phosphate. As a result of secondary infection by urea-splitting organisms a primary calculus of any composition may acquire an external coating of calcium phosphate and magnesium ammonium phosphate and have the external appearance of an alkaline infection stone. The non-calcium-containing calculi are composed of uric acid and cystine and occur in an acid urine.

The nucleus of a calculus is that portion formed first and upon which further precipitation occurs to produce growth of the stone. It may be of different composition from the rest of the stone. Nuclei originate in 2 ways:

1) As plaques (type 1 lesion of Randall) beneath the epithelium of the renal papilla which become exposed to the supersaturated urine of the calyx with resulting stone growth. Such calculi have a typical asymmetric structure with the nucleus at or near the surface of the stone.

2) By direct precipitation of salts from the urine of the efferent channels (type 2 lesion of Randall). Calculi formed in this manner may have a central nucleus surrounded by symmetrical concentric laminations or they may exhibit great irregularity of structure.

The composition of the nuclei of the various types of stones is discussed. The majority of calcium-containing calculi have nuclei of calcium phosphate. If magnesium ammonium phosphate is present in the nucleus we infer that urea-splitting infection was present when the nucleus was formed.

The influence of urinary pH on the solubility of the stone-forming salts is discussed. The solubility of calcium phosphate is markedly increased in acid urine; each half unit step decrease in pH results in doubling of the solubility of the average amount of this salt present in normal urine over the pH range 7.0 to 5.6. The solubility of magnesium ammonium phosphate is also increased in acid urine. Acidification therapy is, therefore, of value in prevention of calculi of these compositions. Uric acid and cystine become increasingly soluble in alkaline urine; alkalinization therapy is therefore indicated to prevent calculi of these compositions. The solubility of calcium oxalate is practically unchanged over the clinical pH range. Therefore, change in pH is of no value in prevention of calcium oxalate deposition.

Calculi composed of calcium phosphate and magnesium ammonium phosphate formed in the presence of urea-splitting infection will almost inevitably recur unless the infection is eradicated because of the extreme insolubility of these substances in markedly alkaline urine. The clinical implication is discussed.

The presence of a stone nucleus in the urinary tract reduces the ability of the urine to hold its salts in supersaturated solution. To conserve, if possible, this capacity of urine to hold its salts in solution we should endeavor to prevent nuclei from forming by avoiding even transient periods of oliguria in stone-forming individuals.

It is generally considered that there is little that can be done to prevent formation of calcium oxalate calculi. However, the majority of such calculi have nuclei of calcium phosphate which is quite soluble in acid urine. It is suggested that we attempt to prevent calcium oxalate calculi by preventing calcium phosphate nuclei from forming by means of acidification therapy. Resorption of calcium phosphate nuclei located upon the external surface of some calcium oxalate calculi is not infrequently observed and probably occurs in a urine which has become more acid.

Many of the phenomena of stone formation are explainable on the basis of physical chemistry. Clinical considerations suggest that there may still be other, and as yet unknown, factors responsible. It is possible to correlate the structure and composition of calculi with the clinical case history of patients from whom stone was taken. A knowledge of the composition of the nucleus and outer portions of a calculus may be of distinct clinical importance in determining the cause of the calculus and the treatment necessary to prevent recurrence. Illustrative examples are given.

It is predicted that effective regimens to prevent recurrence of stone may be found and it is reasonable to expect that they will be based on physicochemical principles.

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ANALYSIS OF RENAL CALCULI BY INFRARED SPECTROSCOPY

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INTRODUCTION

The importance of a knowledge of the chemical composition of renal calculi is accepted generally.[1] Reliable analytical information is fundamental for a study of the etiology of stone formation and is absolutely necessary for planning medical regimens. While the classical chemical analysis is confronted with a number of difficulties in establishing the composition of stones, two physical methods have recently been found to be most helpful in this effort: the optical and the x-ray methods, discussed by Prien and Frondel.[2]

The widespread acceptance of the infrared spectroscopy as an analytical research tool in many industrial laboratories suggested its use as a new method for the analysis of renal calculi. Infrared spectroscopy had already been used successfully in a similar application, the determination of mineral constituents of rocks.[3-5] The speed and accuracy combined with the convenience of the commercially available infrared spectrometers strongly recommend their application in the clinical laboratory.

PROCEDURE FOR INFRARED ANALYSIS

A double beam recording infrared spectrophotometer from The Perkin-Elmer Corporation, Norwalk, Conn. was used in these studies (fig. 1). The infrared radiation emitted from a Nernst glower leaves the glower housing at the right side of the instrument in the form of two parallel beams of equal intensity. One beam passes through the sample and the other beam serves to compensate the absorption of infrared radiation by water vapor and carbon dioxide on the way from the source to the monochromator which is housed under the recording drum. The infrared spectrum from 2 to 15 microns wave length can be recorded with a sodium chloride prism in the monochromator. The pen system of the recorder indicates directly the transmittance in per cent transmission of the sample. Usually, the spectra were scanned from 2 to 15 microns in 20 minutes. This time can be shortened if necessary.

The samples were prepared by the mulling technique. A small piece from a desired region of a stone (central nucleus, layers) or a sample of a reference substance was ground with the mulling agent, usually mineral oil, to form a paste with a very fine particle size. This paste was squeezed between two windows of the microcell to a desired thickness. This thickness cannot be controlled

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[1] Panel discussion on urolithiasis. Urological Survey, 4: 2-65, 1954.
[2] Prien, E. L. and Frondel, C.: J. Urol., 57: 949-994, 1947.
[3] Hunt, J. M. and Turner, D. S.: Analytical Chemistry, 25: 1169-1174, 1953.
[4] Hunt, J. M., Wisherd, M. P. and Bonham, L. C.: Analytical Chemistry, 22: 1478-1497, 1950.
[5] Keller, W. D., Spotts, J. H. and Biggs, D. L.: Am. J. Science, 250: 453-471, 1952.

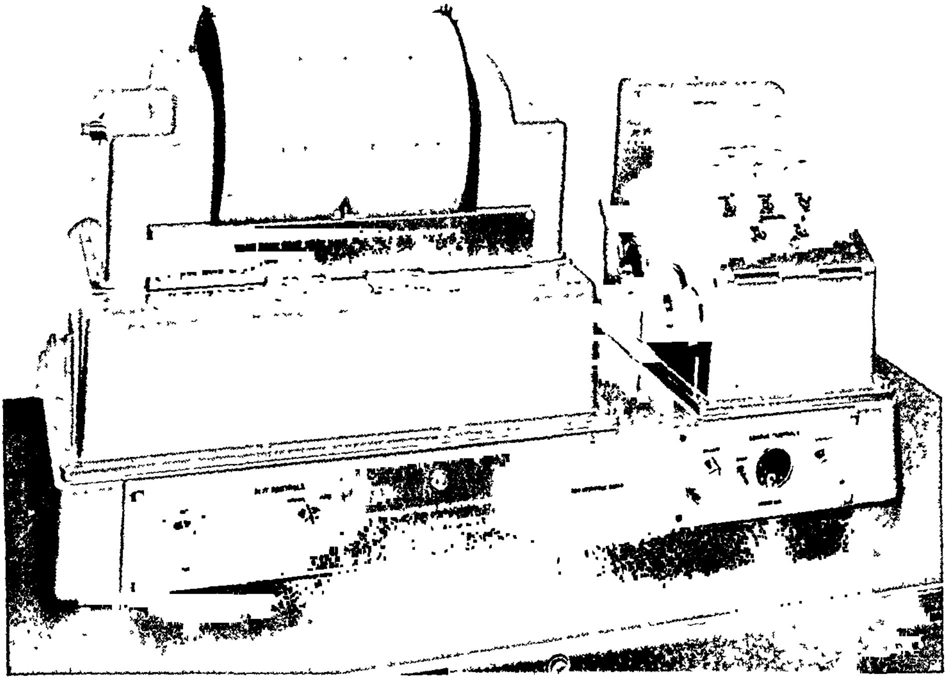

FIG. 1. Double beam recording infrared spectrophotometer

accurately, but with some practice adequate sample films can be produced for qualitative and semi-quantitative analysis. Less than 5 milligrams solid substance are adequate to cover the exposed area. The sample can be recovered after the test if necessary.

The renal calculi examined by this method were of recent origin and not museum specimens. They were analyzed by flame photometry and chemical methods. In addition infrared spectra of characteristic components of renal calculi served as references. Some of these reference materials, such as calcium oxalate monohydrate, dibasic calcium phosphate dihydrate, tertiary calcium phosphate, uric acid and cystine were used in the form of commercially available products of highest purity. Other materials were synthesized. Magnesium ammonium phosphate was prepared by the method usually applied in analytical chemistry to determine magnesium or phosphorus. Hydroxy apatite was gained from a neutral calcium chloride solution mixed with ammonium phosphate in the presence of ammonium chloride and ammonia. The precipitate was analyzed after a week's crystallization time. It gave an "apatite pattern" of x-ray diffraction and had a molar calcium: phosphorus ratio of 1.5 lying between the approximate limits of 1.33 and 2.0 for hydroxyapatite.[6] For the preparation of carbonate apatite an addition of ammonium carbonate was made to the substances forming hydroxyapatite. The monohydrate of calcium oxalate was prepared following Schmidt[7] as precipitate from a neutral solution of calcium chloride by an excess of ammonium oxalate.

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[6] Neuman, W. F. and Neuman, M. W.: Chem. Rev., **53**: 1–45, 1953.
[7] Schmidt, N. Ann., **97**: 240, 1910.

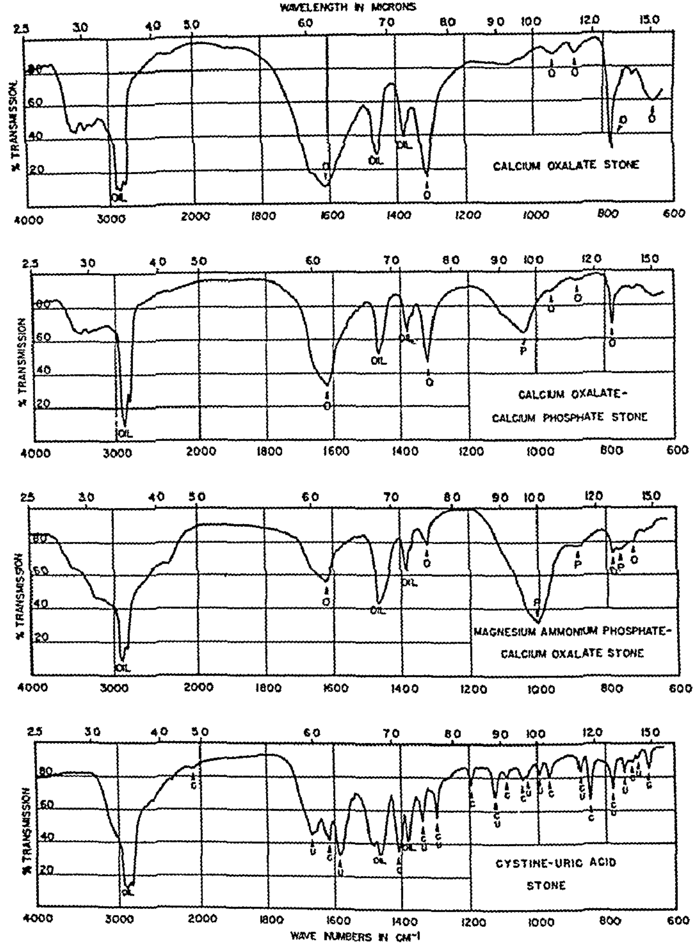

FIG. 2. Comparison of infrared spectra of four renal calculi

RESULTS

The infrared spectra of parts of several renal calculi are reproduced (figs. 2 and 3). They represent a selection from about fifty similar spectra of calculi which had been analyzed previously by flame spectrometry and chemical methods. Such a collection of infrared spectra of analyzed stones served as reference in the identification of unknown stones. An identification template

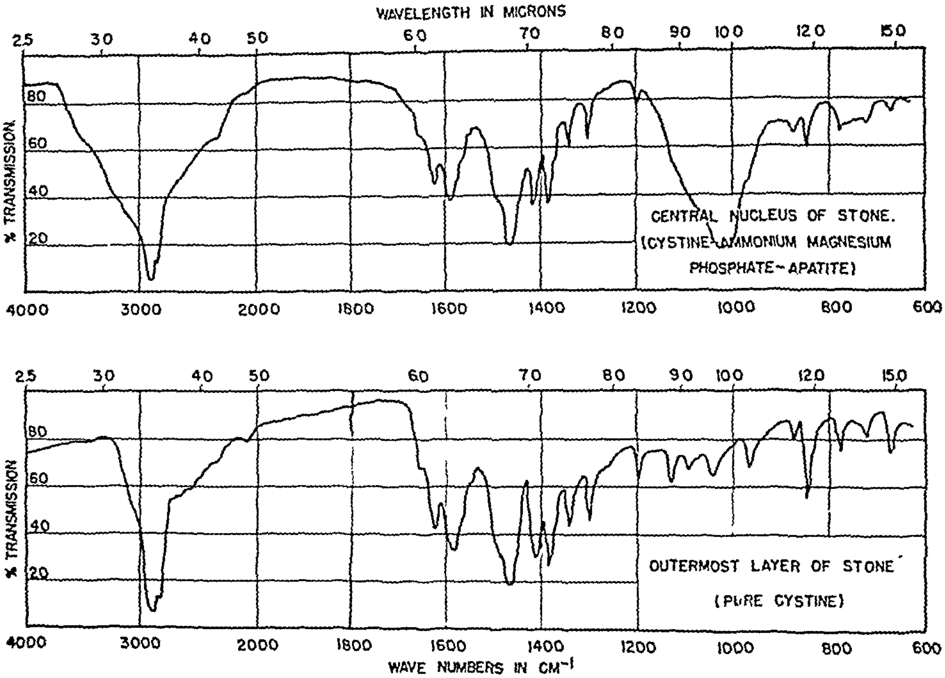

FIG. 3. Infrared spectra of different parts of a stone demonstrating the varying chemical composition.

(fig. 4) in which the infrared spectra of the major components of renal calculi are assembled, was of further help in the identification of the components which are usually found in renal calculi. The spectra in this template were gained from commercially available pure chemicals or products synthesized as described above. These spectra were verified by comparison with published data (apatite,[5] calcium hydrogen phosphate,[8] phosphorus compounds,[9] calcium oxalate monohydrate,[4] uric acid,[10] cystine[10]).

The chemical analysis of the calcium oxalate stone (fig. 2) indicated a small but definite amount of phosphorus which corresponded to an apatite concentration of about 1 per cent. The presence of apatite is noticeable by a slight dip of the spectral curve around 9.5 microns. The wide absorption band of phosphates between 9 and 10 microns limits the minimal amount of apatite which can be recognized in a mixture to about one per cent.

According to chemical analysis the calcium oxalate-calcium phosphate stone (fig. 2) was a mixture of equal parts of calcium oxalate and calcium phosphate in the form of hydroxy apatite. The intensities of the absorption maxima characteristic for the two components vary in binary stones according to the proportion of the components in the mixture. With some experience semi-quantitative conclusions about the composition of the binary mixtures can be reached. Further information about the quantitative evaluation of the infrared spectra of stones will be discussed later.

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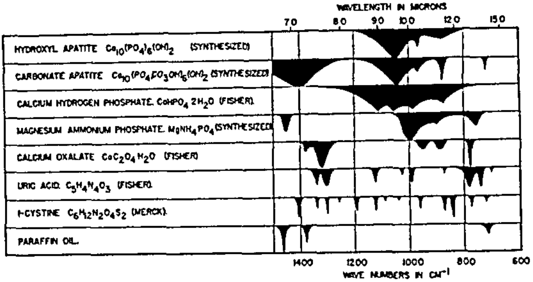

FIG. 4. Identification template with infrared spectra of major components of renal calculi.

The chemical analysis of the third stone (fig. 2) gave a composition of 85 per cent magnesium ammonium phosphate and about 15 per cent calcium oxalate. The maximum of the absorption of magnesium ammonium phosphate is slightly shifted to longer wave length compared with the maximum found in the spectra of apatite. This shift is sufficient to identify the presence of magnesium ammonium phosphate. The close proximity of the broad maxima of absorption of the two phosphates makes the detection of a small amount of one component in the presence of a large amount of the other component difficult. However, 5 per cent of apatite could be detected in a magnesium ammonium phosphate stone.

A stone composed of both cystine and uric acid (fig. 2) represents an example of the convenient identification of calculi with this kind of components. The chemical analysis of this stone had demonstrated the presence of cystine and uric acid in about equal amounts.

The small amounts of substance necessary for infrared analysis favor a study of the development of calculi from a nucleus to a stone with a number of layers. The stone in figure 3 started from a nucleus composed of cystine and magnesium ammonium phosphate with a small portion of hydroxy apatite. The percentage of hydroxy apatite increased in the middle layers. The infrared spectra of these layers are not shown in figure 3. The outermost layer of this stone (fig. 3) was composed of pure cystine.

DISCUSSION

The empirical qualitative identification of urinary calculi by infrared analysis follows the general principle of comparing their spectra with the spectra of known compounds. Certain limitations of this procedure as far as they concern the analysis of urinary calculi have to be discussed.

A separation of the mono- and di-hydrate of calcium oxalate, which is easily accomplished by optical analysis in the visible light, was not yet possible by infrared analysis. The synthesized pure hydrates, including the tri-hydrate, showed the same infrared absorption spectra. The absorption bands observed in the spectrum from 2 to 15 microns are connected with vibrations inside the oxalate anion and the water molecules. Vibrations between the calcium ion and the oxalate ion or the water molecules and the two ions which could be used for an identification of the different hydrates are located in the far infrared, inaccessible to the instrument used in this study.

The phosphate spectra of urinary calculi also need some discussion. The maximum of the absorption at about 10 microns is connected with vibrations inside the PO_4-group. These vibrations are not influenced noticeably by the presence of an OH-group in the slightly basic calcium phosphate with apatite lattice. Synthetic hydroxy apatite and commercial tertiary calcium phosphate showed practically the same infrared absorption. The influence of the OH-group on the rest of the anion in the hydroxy apatite may be concealed by the wide extension of the maximum at 10 microns. Since it was established by x-ray studies[2] that the PO_4-group in calcium salts of renal calculi is present in the form of a basic calcium phosphate, an absorption maximum at 9.65 microns is considered an indication of the presence of hydroxy apatite.

Figure 4 includes the infrared absorption spectrum of synthesized carbonate apatite. The broad maximum at 7.1 microns and weaker maxima at 11.4 and 13.9 are characteristic for the presence of calcium carbonate, very likely bound in the stone in the form of apatite. The carbonate apatite spectrum may be considered as a superimposition of the absorption spectra of tertiary calcium phosphate and calcium carbonate. No mutual influence of the PO_4 and CO_3-ion in the apatite molecule could be observed in the infrared spectra.

The influence of the cations on the position of the PO_4-absorption maximum is well observable. The dislocation of the PO_4-maximum from 9.65 microns for the calcium compound to 10 microns in the magnesium ammonium phosphate was already mentioned as a means to distinguish between these two compounds. Some weaker absorption maxima in the infrared spectrum of magnesium ammonium phosphate can be associated with vibrations inside the NH_4-group. They may serve as further means of identification of magnesium ammonium phosphate.

The spectrum of calcium hydrogen phosphate dihydrate (secondary calcium phosphate) readily distinguishes this compound from the tertiary phosphate. The template (fig. 4) shows a broad absorption maximum with several submaxima. Since $CaHPO_4$ is a rather uncommon phosphate in urinary calculi no stones with this compound were available for analysis.

Cystine and uric acid can be easily recognized by the great number and the position of the sharp maxima in the infrared spectrum of renal calculi with these compounds.

The infrared spectra of all calculi were carefully searched for the presence of absorption maxima which could have been associated with the presence of organic matrix substance. The failure in finding a spectrum of such a substance is understandable considering the small amounts and the poor chemical characterization in which these substances can be expected.

Summarizing the attempts of a qualitative analysis of renal calculi by infrared spectroscopy the following considerations may be appropriate. In the infrared range of 2 to 15 microns the main interest concentrates on the "internal" vibrations of polyatomic ions. These are essentially due to vibrations of atoms relative to a central mass which may be considered at rest. In the case of the PO_4 or CO_3 -ions the central P or C-atom is at rest and the 0-atoms vibrate relative to the central atoms. These vibrations are responsible for the broad maxima observed. They may be modified by other atoms or ions in the lattice as in the case of magnesium ammonium phosphate. The "lattice" vibrations in which the metal ion vibrates in relation to the complex anion cannot be observed in the spectral range used in these experiments. Under these conditions *the infrared spectrum furnishes information essentially about the anions* present in stones, modified to some extent by the cations. This information combined with the knowledge already available from x-ray studies of the lattice arrangement of anions and cations in calculi[2] is sufficient to evaluate the spectra effectively.

Compared with all the other methods used in stone analysis the infrared analysis furnished a permanent record in a very short time. No special training or skill is necessary to handle the infrared spectrophotometer. It is an ideal method for analyzing small fractions of calculi in a short time. To the extent to which other clinical applications of the infrared method will be worked out a greater number of these expensive instruments will be available in clinical laboratories to meet the need of the urologist in routine analysis. This reliable analytical method will also be very valuable in a study of the etiology of stone formation.

In the near future the instrument will furnish quantitative information on the composition of solid materials. In a new procedure the stones or parts (nucleus and various layers) will be ground to a fine powder. A known quantity of this powder will be mixed with solid potassium bromide and pressed to form a platelet. The infrared spectrum of this platelet will give quantitative data for the composition of stones. The information gained in the above described mulling technique is only semi-quantitative. However, it will in many cases already satisfy the needs of the urologist and others interested in concretions.

SUMMARY

The infrared spectra of mulled renal calculi are useful in the qualitative and semi-quantitative identification of the components of stones. An identification template with the most common components of renal calculi is presented. Permanent analytical records may be obtained from small samples (5 mg.) in a short time.

The author is indebted to Drs. A. J. Butt and R. H. Leonard for the stone specimens and their interest, and to W. H. Harold for technical assistance. The project was supported by the Butt-Douglas Research Foundation under contract with the Office of Naval Research.

ALUMINUM GEL DIETARY PROPHYLAXIS AFTER EXTENSIVE NEPHROLITHOTOMY

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The high incidence of recurrence of calculi following extensive nephrolithotomy is well known.[1, 2] In 1945 Shorr[3] suggested the use of aluminum gels in conjunction with a diet in which the phosphate content is moderately low to prevent the recurrence of phosphatic calculi. Subsequent clinical studies indicated the effectiveness of this program.[4, 5] To further evaluate the effectiveness of Shorr's regimen it seemed apporpriate to review the cases of extensive nephrolithotomy performed at the New York Hospital. Only those cases in which the stone analysis revealed high phosphatic content were included. All of the stones in this series were large, branching, radiopaque, and composed of varying amounts of calcium, magnesium, and ammonium phosphates and carbonates. Eighteen consecutive operations for the removal of such stones were performed on the Cornell Urological Service of the New York Hospital between 1946 and 1953. In 12 instances the nephrolithotomy involved complete renal bisection, while the remaining six kidneys were opened for at least two-thirds of their length. The urinary culture was positive in sixteen, sterile in one, and not done in one. The bacteria grown in the cultures of urine were Proteus vulgaris in 3 cases, mixed staphylococcus and streptococcus in 3 cases, and coliform organisms in the remaining specimens. The patients, 10 males and 8 females, averaged 47 years of age, the oldest being 64 and the youngest 27. The right and left kidneys were operated on 10 and 8 times respectively. The voided urine was alkaline in 14 cases and neutral or slightly acid in four.

The operation employed was similar to that described by Slaughter.[6] The renal pedicle was dissected free and occluded by a rubber tourniquet. The kidney was then split in the general location of Broedel's line and the stones were removed. We have not hesitated to leave the vascular supply occluded for 30 to 40 minutes continuously, and on a few occasions as long as 1 hour. In most instances the tourniquet was released periodically for several minutes to permit the circulation to return. After the stones had been completely removed the

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tourniquet on the renal pedicle was released intermittently to permit identification of the major severed vessels, which were then transfixed with fine catgut sutures. The renal halves were approximated and held together by mattress sutures of chromic catgut placed at right angles to the convex border of the kidney. Strips of moistened ribbon catgut were placed under the loops of the mattress sutures. Slaughter suggested placing a superficial row of capsular sutures but we have not done this routinely. A nephrostomy tube was inserted in each of the kidneys. Since major blood loss was always anticipated, transfusions were begun early in the procedure. The average blood given was 1500 cc, varying from 3,500 cc to 250 cc. All but 5 patients had a marked drop in blood pressure some time during the procedure.

In the immediate postoperative course the nephrostomy tubes were left on straight drainage and were only irrigated to insure their patency. After the first week, gentle daily irrigations with saline or Suby's solution G were usually employed. The nephrostomy tube was removed about the twentieth postoperative day. As soon as the patient was able to eat a general diet he was placed on the Shorr regimen.

Major postoperative hemorrhage occurred in four instances; one subsided spontaneously after the administration of transfusions; the remaining three required nephrectomies on the ninth, tenth, and thirteenth postoperative days respectively. Bloody drainage from the kidney was routinely observed. Transient uremia, with an elevated blood urea nitrogen to 80 mg. per cent or more, occurred in 3 patients. Calculus fragments were left behind in 2 kidneys, while radiographically there was no evidence of residual stone in the other 16 kidneys. Since 3 kidneys were removed and one was lost to follow-up, there remained fourteen postoperative kidneys to be observed for possible recurrence or growth of stone.

One patient (NYH 78981) was not placed on the Shorr program and a new stone appeared in the postoperative kidney within 3 months. The regimen was then instituted and 2 years later the stone, which had not increased in size, was surgically removed. On the program, the patient has had no further recurrence in the subsequent 3 years. A chronic alcoholic patient (NYH 227142) had all stones removed from the *left* kidney in 1946 but had not adhered to the regimen (as established by the patient's admission and by examinations of the 24-hour urines for calcium and phosphorus content). Stones recurred in the left kidney by the ninth month. All stones were then removed from the *right* kidney in 1950, but again the program was neglected and recurrence of stones was observed by the second month. The prophylactic therapy was then instituted under accurate supervision and in the succeeding 6 months there was no further stone growth. Hess made a similar observation on a patient with bilateral staghorn stones. Each time the program was assiduously followed, no stone growth was observed; otherwise, rapid bilateral enlargement was detected.

Radiographically, the 11 remaining kidneys demonstrated neither recurrence nor growth of any residual calculus. All of the 11 patients were carefully regulated on the Shorr program, which included periodic determination of phosphate output in the 24-hour urine specimen. The longest period of follow-up was 7 years, the shortest 1 year, with an average of 3 years.

DISCUSSION

These results are at variance with the previous observations regarding the recurrence of renal phosphatic calculi following extensive nephrolithotomy. Brady[2] reported a recurrence rate of just over 75 per cent, while Twinem[1] reported a 40 per cent recurrence following fifteen extensive nephrolithotomies.

It is not our purpose to advocate freely complete nephrolithotomy in all cases of staghorn renal disease. However, the observations from this and previous studies (Marshall and Green) do indicate that if such extensive surgery is carried out it should be followed by conscientious application of the aluminum gel dietary program. This prophylactic plan requires the time and effort of the patient, the physician, the dietitian and an analytic laboratory to insure good results.

SUMMARY

To establish the effectiveness of the aluminum gel dietary regimen in the prevention of renal phosphatic calculi, eighteen extensive nephrolithotomies for the removal of typical staghorn calculi have been reviewed. Fourteen of these cases were followed for growth or recurrence of stone for periods varying from one to seven years postoperatively. In no instance did a new stone appear or a residual fragment grow while the patient was definitely following the program. In some instances defection from the prophylaxis promptly resulted in a recurrence. The postoperative recurrence rate in other series in which the regimen was not stressed has generally been high.

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CALYCEAL DIVERTICULUM

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The calyceal diverticulum has been considered an uncommon entity and its clinical significance has been frequently neglected. We wish to report 14 cases seen on our service and an additional 5 cases that have come to our attention. A review of the literature has yielded 82 cases of calyceal diverticula or conditions we believe to be calyceal diverticula. Undoubtedly, additional cases have been reported but escaped our attention due to the confusing terminology associated with this condition, or were reported in the foreign literature. In our experience calyceal diverticulum has occurred frequently enough to warrant consideration, and in 11 cases significant symptoms existed to necessitate definitive treatment.

TERMINOLOGY

Since the first description of a calyceal diverticulum by Rayer in 1841, the terminology of the condition has been confusing because of the multiplicity of terms coined by authors on the subject. Some terms describe the same condition, while others have been introduced to denote slight variations of the basic lesion. Calycine cyst, pyelogenic cyst, hydrocalyx and pyelosynaptic cyst have been employed in discussing this subject. Prather first introduced "calyceal diverticulum" and we are of the opinion that this is an appropriate term. A calyceal diverticulum is considered to be a urine-filled cavity lying peripherally to a calyx, and communicating by means of a small channel with the calyx, the epithelium of all the structures involved being of a transitional cell type. Contrary to some writers, we are of the opinion that this classification includes all transitional cell lined diverticula of the renal collecting system in which there is no obstructive factor present, such as a calculus, or inflammatory reaction. Abeshouse uses pyelogenic cyst to describe a transitional cell lined cavity lying peripheral to the renal pelvis, communicating through a pinpoint opening, rather than a distinct channel. Others have used this term synonomously with calyceal diverticulum. We have not encountered such a lesion, but are of the opinion that such a condition represents a variation of a calyceal diverticulum and is best considered as such.

ETIOLOGY

The etiology of a calyceal diverticulum is not known. Many consider the condition to be embryological aberration. Supporting this opinion is the similarity of the epithelium in the adult kidney and the calyceal diverticulum, suggesting a common embryological origin. Narath in his excellent monograph discusses

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the embryology of the kidney in detail, describing the division of the future renal pelvis into orders, the first order comprising the future major calyces, the second order the minor calyces and so on, to possibly the fifteenth order. The higher orders persist as the collecting tubules of the adult kidney, while the lower (presumably the third and fourth) orders degenerate. Should a segment of the lower order fail to degenerate, the persistence of the structure could conceivably lead to the formation of a calyceal diverticulum.

Moore, Watkins, Winsbury-White, and others have pointed to calyceal achalasia as a possible cause of calyceal diverticulum. Referring again to Narath, there has been described a well defined system of sphincters about each calyx which facilitates filling and emptying of the calyces in a definite synchronized manner. Those adhering to the acquired origin of the calyceal diverticulum suggest that as other tubulomuscular structures develop achalasia, so may a calyx. Achalasia of the calyx results in chronic ineffectual emptying, leading to progressive dilatation behind the sphincter, and subsequently a calyceal diverticulum is formed.

Examination of the surgical specimen has revealed an absence of significant inflammatory reaction about any of the component parts of the calyceal diverticulum. The communicating channel usually is free of significant scarring which may have led to its formation. Inflammatory reaction of the mucosa of the channel and the diverticulum is usually associated with infected urine and calculus formation. These facts tend to suggest embryological defects as the origin of the diverticulum. We are in agreement with others that the calyceal diverticulum is of an embryological origin.

SYMPTOMS AND DIAGNOSIS

There are no distinguishing clinical features of a calyceal diverticulum. While pain has been the most prominent presenting complaint, the wide range of severity and type prevents classification attributable to a single entity. In our series pain varied from a low grade chronic pain in the costovertebral angle to sudden severe colic type. Symptoms secondary to infection such as frequency, dysuria and hematuria were seen in our series and supported by clinical evidence. In general, the calyceal diverticulum produces symptoms similar to other urinary tract diseases and the diagnosis is made only after a careful study of the patient.

The age and sex incidence of calyceal diverticula does not appear to be a significant factor. In our series the ages ranged from 20 to 62 years. Weyrauch and Fleming reported what we believe to represent a calyceal diverticulum in a 2-day-old infant. The sex distribution in reported cases is about equal. There does not appear to be a significant incidence of the side involved or the pole affected although diverticula of the middle calyx has been noted only twice, one in another report and case 19 in our series.

The diagnosis of calyceal diverticulum is made by x-ray findings. Demonstration of a saccular structure communicating with a calyx by means of a narrow channel is presumptive evidence for the diagnosis. While excretory uro-

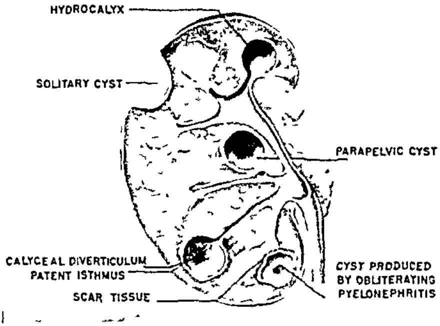

FIG. 1. Differential diagnosis of calyceal diverticulum

grams are adequate in most cases, occasionally retrograde pyelography may be necessary to demonstrate the lesion. Calculi are seen in about 50 per cent of the cases. There may be a solitary calculus or there may be multiple small calculi within the diverticulum. On the plain film the somewhat peripheral location of the calculi may suggest the possibility of a calyceal diverticulum, but of course is not pathognomonic.

The differential diagnosis of the calyceal diverticulum includes hydrocalyx, localized obliterating pyelonephritis, parapelvic cyst, simple cysts, and tumor (fig. 1). *Hydrocalyx* is a dilatation of a calyx due to infundibular pathology, either a calculus or inflammatory reaction. Infundibular changes may be seen on x-ray in a hydrocalyx while in the case of a calyceal diverticulum, this structure is usually of normal configuration.

Localized obliterating pyelonephritis is an inflammatory condition which progresses to complete obliteration of a calyx. As the original authors point out, confusion between this condition and calyceal diverticulum could arise as the calyx becomes narrowed. Only by serial x-rays is it possible to differentiate this condition clinically. *Parapelvic* cyst is a low cuboidal cell lined cyst lying adjacent to, but not communicating with, the renal pelvis. It does not fill with contrast material unless an inflammatory process has caused a communication with the renal pelvis. *Simple cysts* likewise do not communicate with the renal collecting system, and usually lie in the cortex of the kidney, although medullary cysts do occur.

While some authors are of the opinion that calyceal diverticula are small, we have encountered various sizes ranging from 1 cm. to 5 cm. and feel that this feature is of little diagnostic value.

The diagnostic pitfalls of renal tumor are familiar to urologists. Cases 9 and 11 had preoperative x-ray diagnoses of tumor, but were proven to be calyceal diverticula (fig. 2).

The positive diagnosis of calyceal diverticulum can only be made at the operating table or by careful pathological study of the surgical specimen which

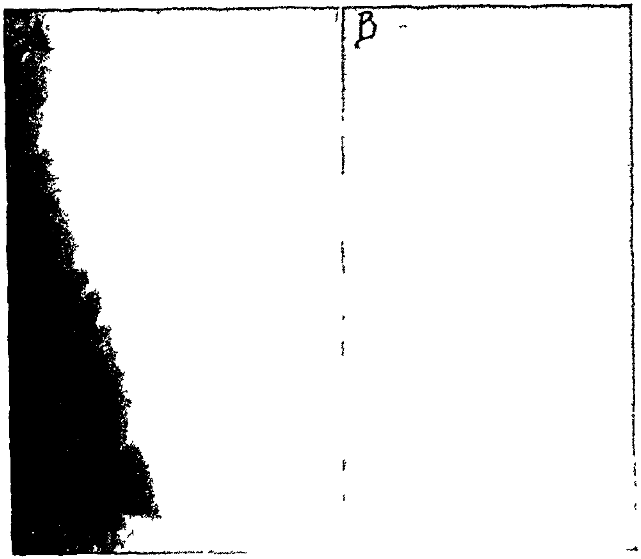

FIG. 2. *A*, case 9. Preoperative diagnosis of renal tumor. At operation, calyceal diverticulum was found.

B, case 11. Preoperative diagnosis of renal tumor. At operation, calyceal diverticulum was found.

demonstrates a transitional cell lined cystic structure communicating with a calyx by a narrow channel which also is lined by transitional cell epithelium.

TREATMENT

The management and treatment of a calyceal diverticulum are governed chiefly by the symptomatology and associated disease. In the asymptomatic case, without pathological elements in the urine, observation is indicated. The potentiality of infection and stone formation should be borne in mind. Periodic evaluation including careful urinalyses and either intravenous urography or retrograde pyelography is indicated. In patients presenting intermittent pyuria, or persistent pyuria, the use of chemotherapeutic agents or antibiotics will only afford temporary relief. As with other obstructive lesions of the genitourinary tract, correction of the underlying pathological process is the treatment of choice, when possible.

In those cases with symptoms, persistent abnormal urine and x-ray evidence of stone formation, we feel that surgery is indicated. The exact procedure used in treating calyceal diverticula varies in different reports. Beneventi reports success in his case by periodic dilatation of the communicating channel of the diverticulum using ureteral dilators through the cystoscope. This was possible in his case which was located in the upper pole but it would probably be impossible in patients having a calyceal diverticulum of the lower or middle minor calyces. Following successful dilatation of the narrowed isthmus, a potential abnormal pocket still remains, and it would seem that in cases treated in this manner recurrence would be likely. Prather reports good results in excising the dome and upper portions of diverticulum lining, then dilating the communicating channel. In his first case he approximated the kidney without nephros-

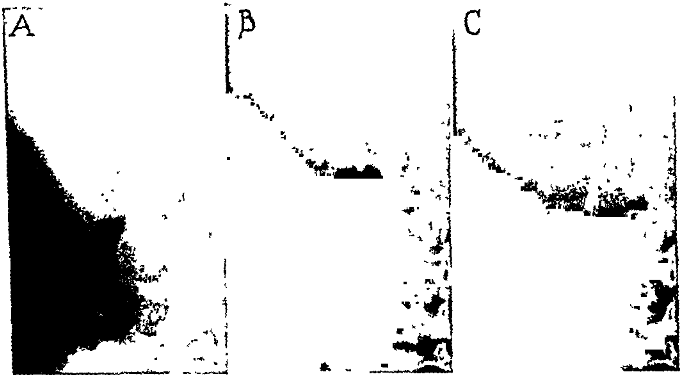

FIG. 3. Case 1. *A*, preoperative x-ray showing cluster of small calculi in calyceal diverticulum of upper right calyx. *B*, excretory urogram. *C*, postoperative excretory urogram.

tomy while in the other cases he inserted a nephrostomy tube through the previously dilated communicating channel. The nephrostomy tube was removed 2 weeks later in 1 case, and 3 weeks in the other. Newman, et al. used a similar procedure with good results. Engel reported good results in 2 cases treated by partial resection of the portion of kidney involved. Wyrens also suggested a procedure of this type.

The treatment of a calyceal diverticulum is twofold: eradication of the diseased portion and conservation of normal renal tissue. Our treatment consists of complete excision of the diverticulum lining and obliteration of the communicating channel. The diverticulum is exposed through a nephrotomy incision, and by sharp and blunt dissection the wall is carefully removed. The communicating channel is obliterated by fine atraumatic chromic sutures. Bleeding from the renal tissue is controlled by individual ligatures. The divided edges of the kidney are then closed by deep hemostatic doubled sutures over fat pads. We do not employ nephrostomy drainage. In this manner we feel that we have obliterated the diverticulum with a minimum of damage to functioning renal tissue and recurrence of the diverticulum is unlikely. Figure 3 shows the pre- and postoperative films of case 1 (W. B.). Surgical procedure consisted of excision of the diverticulum lining and obliteration of the communicating channel.

DISCUSSION OF CASES

Referring to table 1 it will be noted that the most common symptom in our series was that of pain on the affected side. Fourteen of the 19 patients complained of pain of some type, and in 7 (cases 2, 4, 7, 10, 12, 15, 16) pain was the only subjective finding. The type and degree of pain varied a great deal, ranging from acute severe colic to that of an annoying intermittent aching flank pain of several months' duration. There was no characteristic type of

TABLE 1. *Tabulation of symptoms and findings in 19 cases of calyceal diverticula*

Case	Sex	Age	Side	Calyx	No Symptoms	Tenderness and/or Pain	Pyuria	Chills, and/or Fever	Colic	Hematuria	Calculi	Surgery
1. W.B.	♂	20	Right	Upper			x				x	x
2. J.M.	♂	27	Left	Lower		x	x				x	x
3. H.F.G.	♂	35	Left	Lower		x	x	x			x	x
4. E.M.	♂	29	Right	Upper		x				x(?)		x
5. J.A.P.	♂	35	Right	Upper		x	x	x	x			x
6. F.W.Jr.	♂	36	Right	Lower							x	x
7. P.A.R.	♂	39	Left	Lower		x					x	x
8. F.McM	♂	30	Left	Upper		x	x	x			x	x
9. E.S.	♂	38	Right	Upper		x			x	x		x
10. W.R.J.	♂	35	Right	Upper		x	x					x
11. A.B.	♀	35	Left	Upper		x			x	x		x
12. R.C.	♂	27	Right	Upper		x					x	
13. H.B.	♂	62	Right	Lower		x	x	x			x	
14. J.G.	♂	30	Right	Lower		x	x	x			x	
15. E.D.	♂	42	Left	Lower		x	x				x	
16. W.C.B.	♂	50	Right	Upper		x						
17. L.C.	♀	31	Right	Upper			x					
18. H.B.	♂	41	Left	Upper	x							
19. J.L.	♂	58	Left	Middle	x							

pain detected which could be attributed to the calyceal diverticulum. Likewise, the localization of the pain was not characteristic. In our series, pain was localized in the costovertebral angle of the affected side, the flank, the lower right quadrant (case 5) and in case 4 the pain was localized in the right upper quadrant of the abdomen. Tenderness was noted in the patients who had colic (cases 5 and 11) and, in addition, costovertebral angle tenderness was elicited in 3 patients (cases 3, 5, 7). Two patients had symptoms referable to the gastro-intestinal tract. E. M. had complete remission of post-prandial eructations and vague epigastric distress following removal of a calyceal diverticulum. Patient J. L. (case 19) had negative gastro-intestinal studies despite chronic gastric symptoms. However, no treatment of his calyceal diverticulum has been carried out.

Calculi were found in 10 cases. Cases 1 and 10 consisted of aggregates of many small calculi, while the remainder consisted of solitary calculi. Despite the high incidence of calculi, only 2 patients (cases 9 and 11) had demonstrable hematuria and these cases did not have calculi. Patient E. M. (case 4) allegedly had "red urine" prior to admission, but this was not found during his hospitalization. Case 5 (J. A. P.) had colic type pain and a calculus was demonstrable; the remaining cases having calculi denied colic type pain. From our experience, it would appear that the presence of calculi does not necessarily precipitate colic or hematuria. These symptoms are most likely the result of over-distention of the diverticulum and the subsequent inflammation of the mucosa due to infection.

Pyuria was found in 10 patients, 5 of whom had sufficient infection to cause chills and fever The degree of pyuria varied considerably, being more severe in cases with calculi However, case 17 was without demonstrable calculi (or other genito-urinary tract disease except the calyceal diverticulum) and the patient continues to have persistent pyuria which has not responded to the various antibiotics

Only 1 patient (case 18) had hypertension and in this case the calyceal diverticulum found in a routine evaluation of hypertension which included an intravenous pyelogram The patient's condition did not warrant further study He did not have any subjective complaints referable to the urinary tract Similarly, in case 18 the calyceal diverticulum was an incidental finding

In conclusion, patients having symptoms referable to the urinary tract or exhibiting abnormal urinary findings warrant careful urologic investigation In the differential diagnosis, the possibility of a calyceal diverticulum should be borne in mind When symptoms and findings warrant, surgical removal of the calyceal diverticulum is advocated

SUMMARY

Nineteen cases of calyceal diverticulum are presented, 11 of which were treated surgically In our experience, this entity has not been a rare one It is possible that calyceal diverticulum is encountered frequently by other urologists but has escaped their notice or the significance of the lesion overlooked All but 2 of our cases had subjective symptoms and objective or clinical findings Theories as to the etiology of calyceal diverticulum are discussed, the authors favoring an embryological origin In our experience the most satisfactory method of treatment has been the total removal of the diverticulum with obliteration of the channel communicating with the renal pelvis Diagnosis of calyceal diverticulum is dependent upon x-ray studies and, where possible, histologic review of the surgical specimen The literature is reviewed briefly and 19 cases added

ADDENDUM

Subsequent to the preparation of this paper another calyceal diverticulum containing two calculi has been encountered and treated surgically as described above In addition, patient H B (case 13) returned for re evaluation and was found to have a left calyceal diverticulum as well as the one on the right previously noted When last seen he was asymptomatic but did exhibit a moderate degree of pyuria

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NEURILEMMOMA (ARISING IN THE HILUS OF LEFT KIDNEY)

CHARLES A. SPEAS PHILLIPS AND GEORGE BAUMRUCKER

The following is a case presentation of a rare type of nerve tumor arising in the hilus of the kidney.

A 56-year-old, white, male police officer had had intermittent fever and chills for 5 years. He has been treated with various antibiotics by his family physician during this time with response on each occasion. The patient stated that during the past 2 years he had noted a dragging pain in the left flank area. During the physical examination, when a large mass was palpated on the left, the patient admitted that he had noticed a fullness in this area for 2 years, but he had failed to give this information to his family physician. There has been no history of hematuria, pyuria, frequency, nocturia, urgency or passage of stones. Although the patient had lost 45 pounds in weight in the last 2 years, he stated that he had been in excellent health, except for the recurrence of fever and chills.

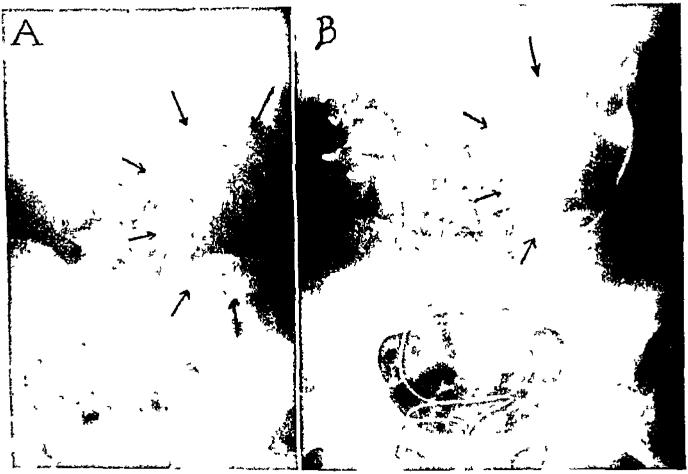

FIG. 1. *A*, plain x-ray showing soft shadow outline. *B*, retrograde pyelogram showing distortion of renal pelvis and lateral displacement.

Blood pressure, 130/76; pulse, 76; temperature, 98.6. The patient was well nourished, well developed, and did not appear chronically ill. Examination was negative except for a mass which was firm, movable, located in the left upper quadrant, and measured 12 cm. in diameter. There was slight tenderness in the left costovertebral angle to deep palpation.

Urinalysis: Reaction, acid; specific gravity, 1.010; no albumin or sugar; no cells or casts. Red blood count, 3,800,000; hemoglobin 11 gm.; white blood

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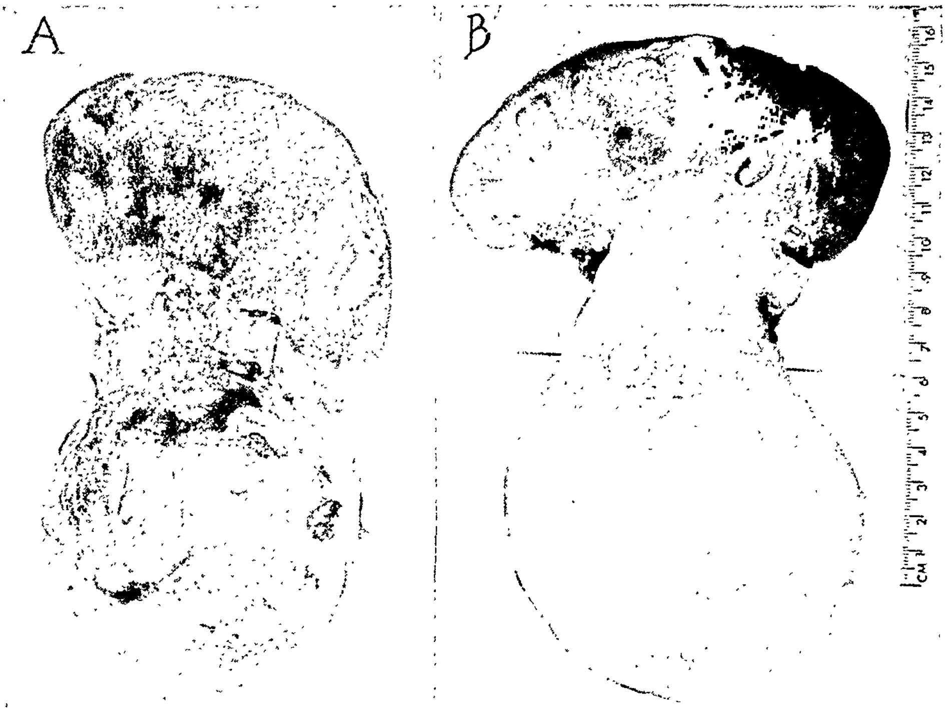

FIG. 2. *A*, gross specimen, anteroposterior view. Note pedunculated tumor attachment. B, cross section showing relation to renal hilus of neurilemmoma.

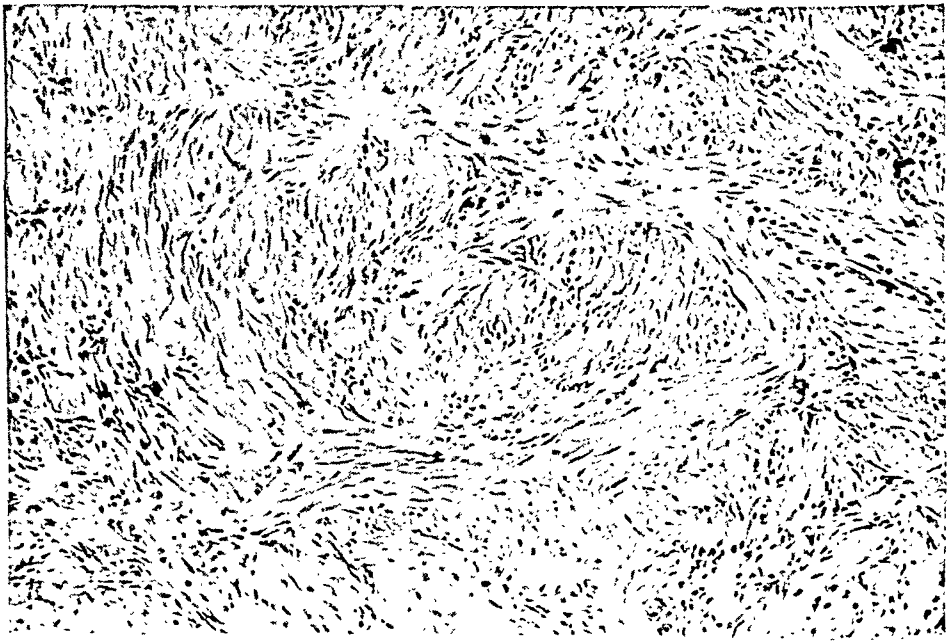

FIG. 3. Neurilemmoma. Low power

count, 10,800; 75 per cent neutrophils; 24 per cent lymphocytes; 1 per cent eosinophils. Sedimentation rate, 25 mm. in 1 hour. Nonprotein nitrogen, 34.4 mg. per cent. Total protein, 8.3 gm.; A/G ratio, 5.5/4.8. Serology negative. Acid and alkaline phosphatase 1.0 and 2.3 Bodansky units respectively. Urine culture showed no growth from the bladder and ureteral specimens. Electrocardiogram was borderline. Chest x-ray was normal. Excretory and retrograde pyelograms showed a normal right urinary tract. On the left there was a large, diffuse, smooth shadow in the region of the hilus (fig. 1) and the lower pole of the left kidney displacing the kidney laterally. The upper calyx was not completely visualized.

Despite the size of the mass, however, the relatively innocuous course of this illness, plus the fact that the mass was movable on physical examination gave the impression that this mass was operable and represented a retroperitoneal tumor arising in the left kidney probably a lower pole malignant nephroma. On March 19, 1954, a left flank incision was made and the entire mass and left kidney were removed without difficulty by Dr. Baumrucker. The mass appeared to arise from the hilus of the kidney. The blood supply was from the renal pedicle. (See figure 2.) Postoperative course of the patient was without complications. Pathology report was neurilemmoma (fig. 3).

DISCUSSION

The neurilemmoma has been called by many names such as the neurinoma, Schwannoma, neurofibroma (although most pathologists feel this term should be used when applied to Von Recklinghausen's disease), and perineural fibroblastoma (this term is best applied to lesions occurring intracranially of which the acoustic neurinoma is an example.) The confusion of these names arises because of the difference of opinion concerning the origin of tumor—whether it is formed by connective tissues or nerve fibers or whether it originates in the sheath of Schwann cells. Whatever the origin, the tumor is benign.

The gross appearance is that of a well encapsulated tumor of soft, rubbery consistency, smooth and regular. On cut section the tumor is pale, grayish-white, and homogeneous except for small and occasional cystic areas. The microscopic appearance is characterized by the palisading of nuclei and interlacing network of wavy, flowing streams of cells. There are usually numerous small degenerated or cystic areas present.

SUMMARY

A case of a neurilemmoma arising in the hilus of the left kidney has been presented. The case history, pathological findings and a brief discussion of the pathology of neurilemmoma have been presented.

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A NEW TYPE OF TUBE FOR URETERAL INTUBATION

MONTAGUE L. BOYD AND GEORGE H. HOLSENBECK

Splinting of the ureter, in patients where ureterotomy is indicated and in some cases of plastic operations on the ureteropelvic junction, is generally accepted as being, I believe, a procedure which is quite successful.

From my own experience and from the articles published on the subject it seems important to use a splinting tube sufficiently large to insure that an adequate size lumen will result from the regeneration of the ureter about the tube. A 14F size appears to be adequate although in one favorable case of mine a good result was obtained by using a 10F polyethylene catheter.

It is, of course, desirable to use a tube which will not become roughened on the outside during the time it is in the ureter. Three to six weeks (an average perhaps of four weeks) is the length of time for intubation, and polyethylene tubing has, I believe, been shown to remain smooth and free of urinary deposits for that long.

But the size 14F polyethylene catheters are quite stiff and no doubt produce a good deal of pressure on the tissues about them before they assume the desirable curves necessary for them to lie in the best position along the ureter and in the kidney and kidney pelvis.

Polyvinyl tubing is so much more flexible, but so far I have not been able to make absolutely sure that polyvinyl tubes possess all the good qualities ascribed to polyethylene, although I find no evidence to the contrary.

Another disadvantage besides the lack of flexibility of using the larger polyethylene tubes (14F) is the effect of pressure on the ureter due to the size of the tube. This is true also of polyvinyl and rubber.

Having in mind trying to avoid trauma to the ureter below the area of ureterostomy I wrote to Mr. Frederick J. Wallace of American Cystoscope Makers, Inc. about a year ago asking him if he could have polyethylene tubes made which were for half their length 14F (for 20 or 25 cm.) with the other half (for 20 or 25 cm.) as small as 7 or 8F, the two ends to be connected by a taper only 1.5 to 2 cm. long.

Dr. Foley, in reply to letters I have sent him, writes me that he uses polyvinyl tubing, and he was kind enough to send me one of the tubes, which is about 14F in size. He brings the tube out through the kidney pelvis and makes a couple of fenestrae in the part of the tube which lies within the pelvis.

I have been accustomed to using an 18F Foley or de Pezzer catheter as a nephrostomy tube and carrying the intubating tube out through the kidney alongside the nephrostomy tube. I leave the nephrostomy tube in for a few days after removing the intubating tube so as to get some idea how successful the operation has been.

For intubation of the ureter I believe that it would be advantageous to have a tube with the following characteristics: 1) a 14F section of the tube to lie in

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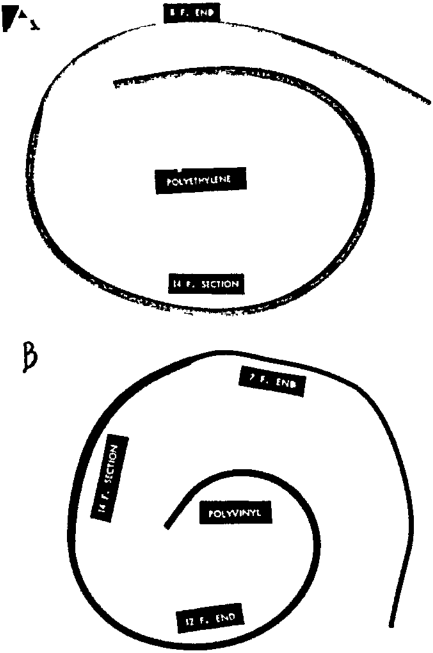

Fig 1 *A*, polyethylene tube with smaller end 8F and larger 14F, length of tapered part is only about 2 5 cm *B*, polyvinyl tube has central part 14F in size about 10 cm long Upper end is 10F in size and 25 cm long Lower end is 7F in size and 18 cm long

the region of the ureterotomy or pyeloplasty incision, 2) with, not only a rather sudden taper from the 14F to 7 or 8F at the lower end, but 3) also, a sudden taper to 10 or 12F at the upper end For practically all cases 8 cm or at the most 10 cm would be long enough for the larger (14F) part of the tube, and with the upper and lower ends 20 or 25 cm long, they would be long enough for any case and could be cut off to obtain any desired length To make such a tube smaller at both ends is possible with polyvinyl but it is questionable whether such a tube or catheter can be made of polyethylene However, if one insists on polyethylene, the 14F upper part could be carried out through the kidney without too much damage to the kidney as I know from experience

I have submitted these ideas to Dr D M Davis and, also, to Dr Frederic E B Foley To have the opinion of such eminent authorities on ureterotomy with intubation and intubation in plastic operations at the ureteropelvic junction seems to be most desirable Dr Davis and Dr Foley both write that they are enthusiastic about the idea

There is another thing which may be of importance in intubation in these cases. At times there seems to be an irritation of the lower ureter where the end of the intubating tube lies. This, of course, would be lessened by having a tube of a smaller size. But I have wondered whether irritation might not also come from changes in the urine or the discharge from the ureteral mucosa, which almost surely must accumulate inside the lower end of the tube. Frequent irrigation to wash out the tube and ureter would probably prevent irritation from this source. Or the lower end of the tube could be sealed. Perhaps dipping the end in hot paraffin would seal the end of the tube, or the tubes could be made with the lower ends sealed if it can be determined just what length or lengths are usually necessary for the lower, smaller end of the tube.

Since submitting our manuscript for publication, Mr. Frederick J. Wallace has sent us some tubes made of polyvinyl which are similar to the polyethylene tube shown in fig. 1, *A*. They are much more flexible than the polyethylene and seem better on that account.

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CYSTOLITHIASIS IN RATS AS INFLUENCED BY HYALURONIDASE, SEX, AND STRESS

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In 1951 Butt[1] advanced the theory that the subcutaneous administration of hyaluronidase might prevent renal stone formation in humans by increasing the activity of the "protective" urinary colloids Reported experiments, particularly those of Vermeulen,[2] have demonstrated that calculous formation in rats may be readily produced by using a foreign body as the nidus It was thought therefore that a study of the effect of hyaluronidase on vesical stone formation in rats might be worthwhile Certain other factors became apparent during the study and were briefly investigated also Although Vermeulen[2] found metallic zinc to be an effective nidus, we hoped to approximate natural conditions as much as possible by using fragments of human calculus as the foreign body

As a pilot experiment 37 young adult rats of the Wistar strain weighing approximately 250 gm each were divided into two groups A, composed of 18 rats, and B, composed of 19 rats A diet of Purina Fox Chow Chequers was fed freely and water permitted ad lib A carefully weighed fragment of a human renal stone of known composition (qualitative analysis indicated calcium 4+, phosphate 3+ and oxalate 1+) was implanted aseptically into each bladder through a suprapubic approach without drainage Group A was used as the control series The rats in group B received a subcutaneous injection of 150 TRU (turbidity reducing units) of hyaluronidase (Wydase) daily for 5 days each week The injected rats were briefly etherized for the administration All animals were sacrificed after 2 months and the bladder contents examined The findings are tabulated in table 1 and they reveal a marked production of calculous material by group A but far less by group B No bacteriological examinations were done but at autopsy the bladders presented no gross abnormality other than the stone

On first consideration the foregoing results appeared to indicate that the administration of hyaluronidase was effective in preventing vesical stone formation A review of the protocols demonstrated that all rats in group A were male and all but two in group B were female Especially impressive was the fact that the largest stones in group B formed in the only two males Accordingly, the difference in results between the two groups might be due to 1) hyaluronidase, 2) sex, or 3) etherization

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[2] Vermeulen, C W , GROVE, W J , GOETZ R , RAGINS, H D AND CORRELL, N O Experimental urolithiasis I Development of calculi upon foreign bodies surgically introduced into bladders of rats J Urol , 64 541–548, 1950

TABLE 1. *Calculous formation in the bladders of Wistar rats: influence of hyaluronidase, but without adequate controls*

Group	No of Rats	Aver. Weight of Stone Implanted†	Total Wgt. of Stone Removed	Aver. Wgt. of Stone Removed	Times Increase
A No hyaluronidase (all males)	18	16.42 mg.	2330 mg.	129.0 mg.	7.8
B Hyaluronidase (all but 2 females)	19	18.80 mg.	686 mg.*	40.3 mg.*	1.9*

* (2 rats were lost so these figures are not absolutely accurate but the tendency would be to lower figures.)

† Calcium phosphate.

In an attempt to evaluate these possible factors, further experiments were carried out. Young adult Wistar rats of approximately 250 gm. each were again used. Two groups of rats, 20 male and 20 female, were used as pure controls, i.e., they were under the same conditions of environment, diet, fluids, etc. as all the other animals but received no hyaluronidase or ether. At autopsy after 2 months no stones were found (three minute albuminous casts were noted). Cultures found a few Escherichia coli from one bladder but the remainder were sterile. The urinary pH ranged from 6 to 7.5. Thus it appears that spontaneous formation of vesical calculi under these conditions must be very rare.

As a second control, B, the bladders of 58 rats, 30 male and 28 female, were implanted with fragments of known weight and composition (qualitative analysis revealed 3+ uric acid and 1+ oxalate) of a human stone. Nothing further was done to this group. After 2 months the weight of the stone had increased 2.2 times in the males but had actually decreased by 90 per cent in the females. As can be noted the stones were essentially the same size and they appeared too large for passage through the urethra. It is interesting to note that the originally implanted stone could not be identified within any calculus found at autopsy; in fact, simple qualitative tests did not detect uric acid in the final product. The pH in 10 males tested varied from 6 to 7.5. Of the 5 male bladders examined bacteriologically at autopsy, two were sterile, two revealed E. coli and one, Strep. viridans. In this and the later bacteriologic studies the specimens were obtained by swabbing the wet bladder at autopsy and using a direct streak plate, an incubated broth tube, and thioglycollate medium. Sixteen female bladders were sterile, 5 contained Streptococcus faecalis, 3 had E. coli (only 1, a pure culture), 2 had microaerophilic Strep., 1 had nonhemolytic streptococcus, 1 had a gram-negative rod (not a Salmonella) and 1 had a Strep. viridans (not pure). Thus there was extreme variation between the two groups but the males, individually and collectively, formed much more calculus than the females, singly or as a whole.

To determine the effect of hyaluronidase, the bladders of 49 rats, 25 male and 24 female, were implanted with fragments from the same stone. This group received a subcutaneous injection of 150 TRU of hyaluronidase each

TABLE 2. *Calculous formation in the bladders of Wistar rats: influence of sex and hyaluronidase*

Group	Males				Females			
	No of Rats	Total Stone Implanted†	Total Stone Removed*	Result	No. of Rats	Total Stone Implanted†	Total Stone Removed*	Result
Pure control, A .	20	0	0		20	0	0	0
Control B	30	300 mg.	701 mg.	+2.3×	28	280 mg.	28 mg.	−90%
Hyaluronidase + ether	25	283 mg.	877 mg	+3.1×	24	308 mg.	0	−100%
Ether	8	128 mg.	600 mg.	+4.7×	9	144 mg.	216 mg.	+1 5×

* Dried three days in air at room temperature

† Uric acid, oxalate stone.

day 5 days a week. These doses would seem to be massive in relation to the size of the animal but what constitutes an effective dose in rats is unknown. Brief etherization was used at the time of the injection. Other than the hyaluronidase injections and the etherizations the conditions were exactly the same as in the preceding section. Of 23 female bladders examined bacteriologically 16 were sterile, 4 contained Strep. faecalis (1 with E. coli), and 3 Strep. liquefaciens. The results shown in table 2 again demonstrate a marked difference according to sex but in comparison with the group B controls no effect of the hyaluronidase was suspected. The increase in stone in the males compared to the control males could have been due to either hyaluronidase or etherization or both.

To determine the effect of etherization, the bladders of 17 rats, 8 male and 9 female, were implanted with fragments of the same stone and these rats were anesthetized with ether briefly five times per week. No hyaluronidase was given and the conditions otherwise were the same. Of 7 male bladders tested, 6 were sterile and 1 contained E. coli. Of the 8 female bladders tested, 2 were sterile, 2 contained hemolytic Staph. aureus and 1 each, hemolytic Staph. albus,

TABLE 3. *Calculous formation in the bladders of Wistar rats: influence of certain forms of stress*

Males

Form of Stress	No of Rats	Total Stone Implanted*	Total Stone Removed
Cold 35°F. .	4	132 mg.	9.0 mg.
Electric shock	5	165 mg.	70.0 mg.
Etherization	5	165 mg.	781.0 mg.

Females

Form of Stress	No of Rats	Total Stone Implanted	Total Stone Removed
Cold 35°F.	7	231 mg.	14.0 mg.
Electric shock	6	198 mg.	36.0 mg.
Etherization .	6	198 mg.	379.0 mg.

* Ammonium magnesium phosphate.

Strep. viridans, Strep. faecalis and a gram-negative rod (not Salmonella). Again there is noted a marked difference in calculous formation according to sex: See table 2. The increase in formation for both sexes compared to all previous results strongly suggests etherization as an enhancing factor. This group is probably too small to permit the conclusion that hyaluronidase did mildly reduce stone formation in the immediately preceding group but the suggestion is present. Certainly the hyaluronidase did not markedly offset the effect of etherization or the natural tendency in males.

Etherization could be considered a form of stress and it did appear to exert a positive influence on stone formation. Consequently a few experiments were carried out to determine the effect of etherization and other forms of stress. The other factors of environment, etc. were kept the same as in the previous experiment except that the fragments used in these experiments came from an ammonium magnesium phosphate human calculus. Three forms of stress were selected: etherization as before, exposure to cold (35°F) for several hours, and repeated electric shocks. These were administered 5 days a week for 2 months and the animals sacrificed as before. Several of the stress rats died, particularly those exposed to cold (those dying were discarded from the tabulations). The results of these experiments are shown in table 3. Although the series was small the evidence is that etherization enhances stone formation in these rats, as it also seemed to do in the earlier studies, while the other forms of stress had no clearly demonstrated effect. Further investigations were not carried out.

CONCLUSIONS

Under the conditions of these experiments, sex was demonstrated to be a principal factor in induced calculous formation in the bladders of Wistar rats, males having a much greater tendency to form stone than females. Calculi must be rare under normal conditions and the presence or type of associated infection did not account for the difference. This tendency predominated over all the other factors studied—including hyaluronidase 150 TRU subcutaneously, brief etherization, and certain forms of stress (all applied 5 days each week for 2 months). Surprisingly, etherization appeared to enhance greatly the formation of stone. The fact that the experiments were designed to demonstrate the usefulness of hyaluronidase against calculous formation but failed to do so may, in itself, be significant.

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CORRELATION OF CIRCUMFERENTIAL LYMPHATIC SPREAD OF VESICAL CANCER WITH DEPTH OF INFILTRATION: RELATION TO PRESENT METHODS OF TREATMENT

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Probably the most significant recent contribution to the problem of bladder cancer was made by Jewett and Strong in 1946.[1] They established present therapeutic and prognostic criteria by a correlation of clinical with pathological findings. This study has been confirmed and extended by Marshall,[2] Colby and Kerr[3-5] and others. Observations from this laboratory have been identical, namely, that there is a definite relationship between depth of tumor invasion of the bladder wall to therapy and prognosis. One of the outstanding conclusions of these clinical investigations is that cancer of the bladder that has deeply invaded the muscularis is usually fatal to the patient if treated by transurethral or segmental resection, radiation therapy, or simple cystectomy (no lymphadenectomy). These reports and subsequent papers have indicated that, potentially, 55 to 84 per cent of cancers that have penetrated approximately *less* than midway through the muscularis are curable if treated by any of the accepted methods as transurethral resection, segmental resection, radiation therapy or cystectomy.

To extend Jewett's important study in a different area, it would be of interest to determine if there is a correlation between depth of growth with circumferential spread of cancer cells within the vesical lymphatics. In addition, data are still lacking concerning the incidence, if any, of patients with noninfiltrating bladder cancer who have tumor cells in regional lymph nodes.

In a previous paper published with Govan and Sawyer,[6] we described the physiological distribution of vesical lymphatics in the dog. It was demonstrated that the lymphatics interlace and cross the midline of the bladder anteriorly and posteriorly. One tenth of a cubic centimeter of a large particle colloidal suspension injected at any site beneath the mucosa disseminated particles in lymphatics throughout 25 to 50 per cent of the bladder circumference within 24 hours. No particles were observed in the mucosal layer. The most distant spread

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Read at meeting of Mid-Atlantic Section of the American Urological Association, Washington, D. C., April 24, 1954.

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within the bladder was constantly noted in the muscle layers rather than adventitia. Even this small quantity of colloidal particles injected in the submucosa produced regional lymph node involvement in 60 per cent of dogs examined. The report now presented of the circumferential spread of cancer within the wall of the bladder and determination of incidence of regional lymph node involvement from bladder cancer that has infiltrated less than 50 per cent of the muscularis is an outgrowth of this preparatory research.

PROCEDURE

A total of 18 bladder specimens were studied from patients with cancer that had varying degrees of infiltration and cellular characteristics. Ten total bladder specimens were obtained by surgery or at autopsy and had cancer penetrating through 50 per cent or more of the muscularis. Five cystectomy specimens were from patients with cancer that had invaded less than half way through the muscularis. Three of these latter bladders were excised 1 to 2 weeks after the tumor had been resected as completely as the transurethral approach permits. The remaining three specimens were each of at least one half the bladder (hemicystectomy) and had been removed for cancer that had infiltrated less than 50 per cent of the muscularis.

The total bladders were inflated with formalin and all specimens were immersed in the same solution. Celloidin embedding, and hematoxylin and eosin

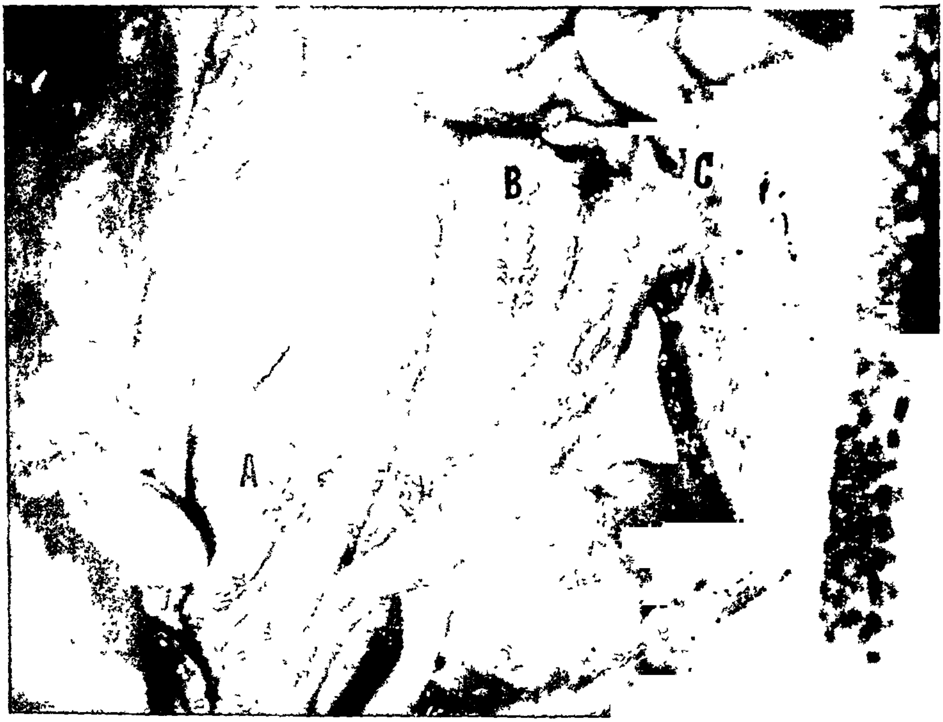

FIG. 1 Lymphadenectomy in region of pelvic brim. Muscles (*A*) cleaned of fat down to fascia. Bifurcation of inferior vena cava (*B*) and aorta (*C*), common iliac, external and internal iliac arteries and veins stripped free of surrounding tissues. Gelfoam used to stop bleeding from tributary entering common iliac vein.

stain were used. Coronal sections were taken through the entire bladder at the level of the tumor.

Lymphadenectomy was performed by the same method in each patient. This consisted in clean stripping of all tissues from the external, internal, and common iliac arteries and veins as well as the terminal aorta and inferior vena cava. In each patient 21 to 60 lymph nodes were excised and studied. After completion of this systematic vascular stripping, all vessels were free of surrounding tissue and could be easily manipulated (fig. 1).

RESULTS

Tumors Approximately 50 Per Cent or Less through the Muscle

Mucosa. No cancer specimens in this series involved only mucosa.

Mucosa and submucosa. Two specimens were examined. In neither instance had the tumor invaded any vesical lymphatics.

Mucosa, submucosa and superficial muscle layers. Three specimens of this type were studied and two had local lymphatic spread within the bladder wall. One of these tumors was sessile and the other a broad-based papillary lesion. Tumor

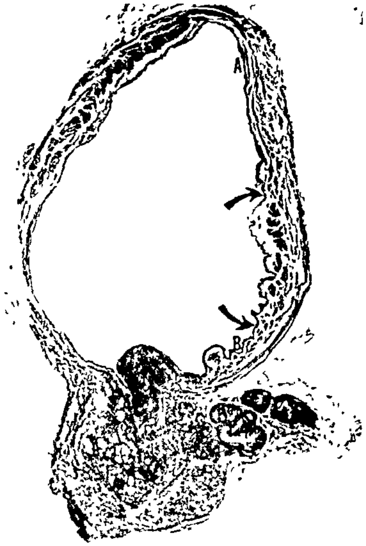

FIG. 2. Saggital sect [illegible] te and seminal vesicles. Cancer involves only mucosa, [illegible] yers. Mucosal size (endoscopic appearance) of tumor i [illegible] xtend circumferentially in the vesical lymphatics to [illegible] tumor-bearing regional lymph nodes present. Routine transurethral resection obviously inadequate. Very generous segmental resection or hemicystectomy probably curative. Lymphadenectomy probably unnecessary.

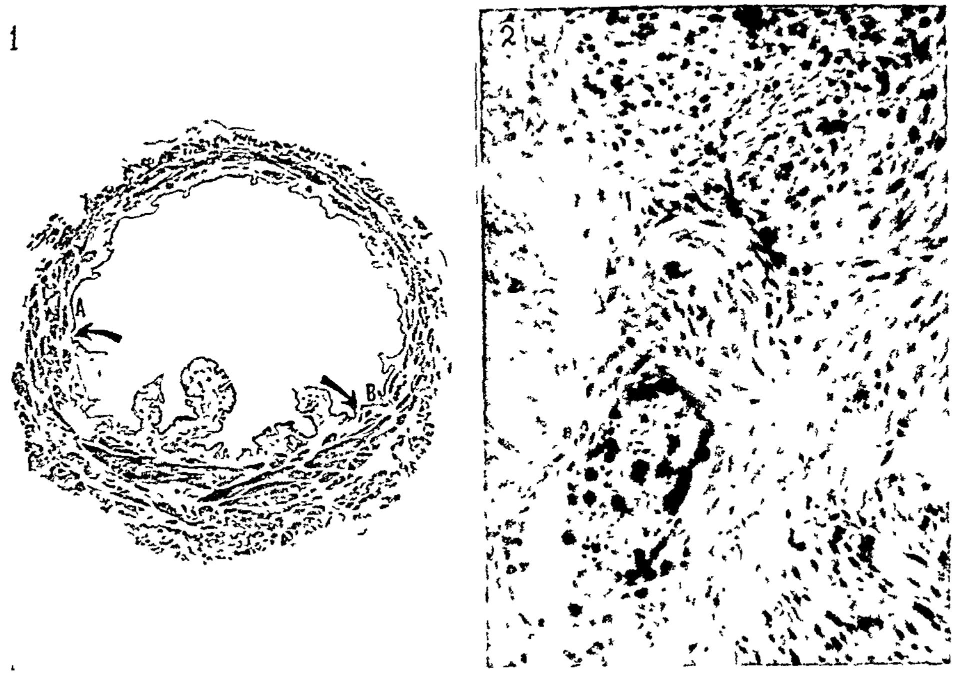

FIG. 3. *1*, Coronal section of bladder Cancer infiltrates only superficial muscle layers except in one small area where about 50 per cent of muscle is invaded. Size of tumor by mucosal appearance is indicated by arrows. Circumferential lymphatic spread is indicated by *A* and *B*. One tumor-bearing regional lymph node. Transurethral resection should be curative, but the significance of lymphadenectomy in this type case is demonstrated. This was the only case of this group with lymph node metastasis. *2*, Section through *1* demonstrating cancer in lymphatics (×425).

cells plugged lymphatics only within the muscularis. Circumferential spread away from the periphery of the lesions was about twice the diameter of the base of the lesions (mucosal size). For example, one tumor base was about 1.5 centimeters in diameter, and tumor cells were observed in the muscularis on either side of the growth totaling approximately four centimeters in diameter. No tumor bearing regional lymph nodes were found in this series (fig. 2).

Mucosa, submucosa and less than about 50 per cent of muscle layers. This group consisted of 5 specimens. It was an unexpected finding to learn that 3 tumors had not invaded vesical lymphatics to any degree appreciably greater than if only superficial muscle fibers were infiltrated. Regardless of deeper muscle invasion of the tumors in this group, only two of the five specimens had marked circumferential spread of tumor cells. All spread was again within lymphatics of the muscularis. None was observed within the adventitia. In the 2 specimens mentioned, the tumor had spread 2 and 6 times the diameter of the tumor base as determined by mucosal size. One of these 5 patients also had an ipsilateral common iliac node containing malignant cells (fig. 3).

Tumors Approximately 50 Per Cent or More through the Muscle

Contiguous local spread did not extend for too great a distance from the gross lesion when referred to endoscopic appearance or palpation of the bladder wall. Within the mucosa, tumor cells did not extend microscopically away from the

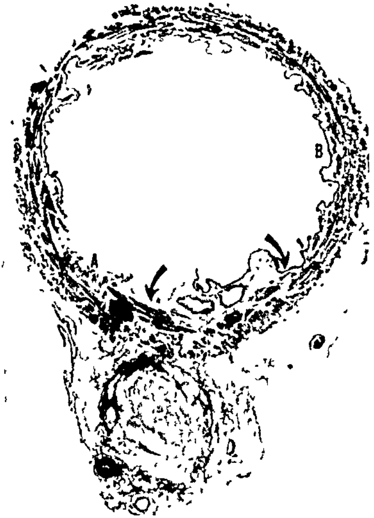

FIG. 4. Coronal section of bladder. Cancer infiltrates through most of muscularis. Size of tumor by mucosal appearance is designated by arrows. Circumferential lymphatic spread is indicated by *A* and *B*. No tumor-bearing regional lymph nodes found. Inadequacies of routine segmental resection demonstrated. Hemicystectomy or cystectomy in conjunction with lymphadenectomy should be curative in this case.

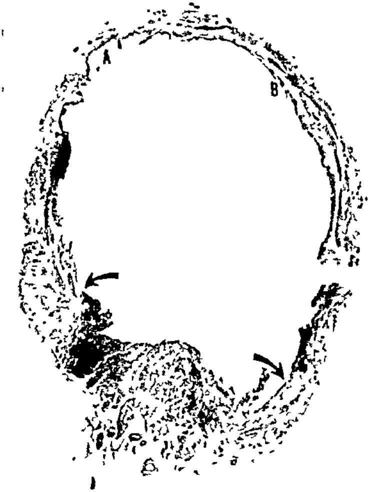

FIG. 5. Coronal section demonstrating cancer infiltrating through entire wall of bladder. Size of tumor by mucosal appearance is indicated by arrows. Circumferential lymphatic spread is shown by *A* and *B*. Eight tumor-bearing lymph nodes found. Futility of segmental resection or hemicystectomy for this type case is obvious.

lesion for more than several millimeters other than could be observed grossly. The greatest spread of cancer cells occurred in lymphatics and between planes of the musculature. The average bladder circumference microscopically involved for this group was about 60 per cent (fig. 4). One specimen with cancer having penetrated through all layers of the bladder, had cancer cells in lymphatics of 90 per cent of the circumference of the bladder (fig. 5). Only one bladder failed to have more than one-third bladder involvement. This was a squamous cell carcinoma of approximately two centimeters in diameter that had invaded the deeper reaches of the muscularis. Lymphatics of the bladder contained cancer cells for only about 20 per cent of bladder circumference. This patient had an ipsilateral common iliac lymph node carrying cancer cells. Eight of the ten patients studied had at least one regional lymph node containing cancer.

DISCUSSION

Too little emphasis has been stressed in published data between mortality after cystectomy due to recurrence of cancer or due to renal disease subsequent to diversion of the ureters. It is true that death from one cause is equally as fatal as death from another. Failure to clearly state the cause, however, does little to increase our knowledge of either aspect of the problem and can unreasonably weight statistics. While cystectomy has been included as effecting the same percentage of cure as more conservative therapeutic procedures for bladder cancer, these figures are probably unjust to the true potential of the operation and must be qualified. In the vast majority of published reports, cystectomy has been used as a "last resort" type of operation when transurethral or segmental resection has failed to cure the lesion. As such, these cases must also be classified as failures of transurethral or segmental resection as well as cystectomy. Of greater concern, however, is the injudicious use of cystectomy in this type patient. In the author's opinion, it amounts to a surgical attempt to cure the surgically incurable.

Where cystectomy has been employed as a first procedure for infiltrative or noninfiltrative bladder cancer, most have been performed without lymphadenectomy or at least there is no mention of the procedure in the reports. It is a rare paper that states that lymphadenectomy was performed and the operative procedure described. There is no common understanding of the term lymphadenectomy. Some urologists employ palpation for enlarged nodes; others explore bifurcation of vessels and excise enlarged nodes; only a few surgeons explicitly state that all regional arteries and veins were stripped clean of adjacent and surrounding tissues. Leadbetter has been a leader in advocating this latter type of complete removal of lymphatics and lymph nodes. Unfortunately, the better statistics produced by this tedious, systematic brand of surgery for infiltrative or noninfiltrative bladder cancer are weighted down by other reports in which only simple cystectomy (no lymphadenectomy) is performed. The decision as to whether cystectomy and lymphadenectomy will be performed must necessarily rest on an integration of other factors: general condition of the patient, age, temperament, status of ureters and renal function, hospital house staff and facilities, experience of the operator, et cetera. This facet of the problem is not under discussion in the present paper. This preliminary report does attempt to correlate the approximately predictable circumferential spread of tumor cells within the bladder for tumors of known depth of infiltration.

From the viewpoint of the urologist, transurethral resection of all bladder cancers is easier, technically, than either cystectomy or segmental resection. In addition the patient has a shorter, smoother, pain-free hospital convalescence. Unfortunately there are several major objections to transurethral resection of malignant tumors. First, the operator is restricted in the extent of his resection by the possibility of perforating the bladder; second, he judges depth of tumor invasion (and hence resection) by the highly subjective norm of visual impression; third, the peripheral or circumferential extent of the lesion and resection is subjectively determined by gross appearance of tumor and "normal" bladder; fourth, no lymphadenectomy is possible with this surgical route. Clinical experience has proven definitely that transurethral surgery is curative for a certain group of vesical cancers. The problem is to accurately determine by biopsy which group of tumors comprise this group.

From the broad aspect of potential curability of bladder cancer, segmental resection is generally to be preferred over transurethral excision as it is possible to remove the entire wall of the bladder at the site of the tumor along with adjacent normal bladder wall. With deeply infiltrative tumors about 60 per cent of the entire circumference of the bladder lymphatics may contain malignant cells. The futility of performing the routine segmental resection with the usual cuff of "normal" bladder is obvious. Tumors of even a less marked degree of infiltration may have locally invaded lymphatics of the muscle far beyond the "cuff of normal bladder."

Segmental resection as routinely practiced implies that the palpating fingers can feel the extent of spread of cancer cells within the bladder lymphatics around the cancer and determine the size of "normal" bladder cuff to be excised with the tumor. This concept of being able to palpate cancer cell dissemination is nearly as untenable as the transurethral approach in which the extent of peripheral and infiltrative spread is determined visually. The classical segmental resection presupposes no regional lymphatic spread as no lymphadenectomy is usually performed. It is readily admitted that lymphadenectomy is difficult and probably impossible to perform properly with the bladder still in the pelvis. It is agreed also that even as now practiced, segmental resection does cure a large percentage of patients with noninfiltrative vesical cancer. In order to increase this percentage rate the data now presented attempt to show, not that the procedure is of little value, but rather to demonstrate by a study of biopsy specimens that a more radical segmental resection is necessary in certain patients.

As a result of the findings of this present study and for the specific indications listed, hemicystectomy has been used routinely. One-third to two-thirds of the bladder is excised with the tumor located in the center of the hemisphere. This frequently necessitates sacrificing one of the ureteral orifices. In these cases, the ureter is reimplanted in the bladder. Six months postoperatively the remaining bladder segment distends to nearly normal capacity. The writer was first acquainted with the excellent functional result obtained following hemicystectomy by Foley in 1952.[7] Prior to bladder closure, lymphadenectomy is performed as completely as possible with the remaining segment of the bladder still in situ. Based on the coronal sections studied, if the tumor is within two to four centimeters of the bladder neck, hemicystectomy is inadequate therapy. If no other serious contra-indications exist, cystectomy is used.

One of the conclusions of this investigation of total coronal sections of the bladder containing cancer is that probably almost the same information concerning the circumferential lymphatic spread of malignant cells could have been obtained by intelligent transurethral resection biopsy of the tumor and "normal" bladder. Correlating collected published data with the preliminary study now presented, the following program appears to be a reasonable and practical method for management of any patient with a bladder tumor, whether opinion is for or against radical surgery.

This program is concerned principally with management of bladder tumors that have infiltrated approximately less than 50 per cent of the muscularis. It is the purpose of this regimen to attempt to increase the present cure rate by more detailed attention to correlation of significant biopsy specimens with the various methods of treatment, and indicate the possibilities of total excision of the cancer. From a practical standpoint the additional time and effort expended by the urologist and the department of pathology is exceedingly small once the program has been organized. The objective of the program is not to champion more radical surgery for bladder cancer. The facts available do not support such a conclusion. Per contra, from the aspect of probable curability of cancer, there is no attempt made to detract from the definite indications for total excision of the bladder. The available data demonstrate also that transurethral or segmental resection *as now practiced* may be inadequate therapy. In summary the tentative program is pointed at definition of specific indications for specific accepted surgical methods. While the rationale, on which the program is based, is valid in that it is a working summary of existing evidence, the writer would be first to alter or discard it altogether in light of new facts.

BIOPSY

All bladder tumors should be biopsied by a resectoscope with the patient under anesthesia regardless of the fact that previous tumors have been only papillomas.

If the size of the tumor base is less than about three widths of the cutting loop, then the entire lesion is completely resected. Deep resection is continued for approximately two loop widths beyond the entire visual periphery of the tumor. As nearly as possible these last pieces of tissue are to be separated from the rest. As each deep cut is made through the base of the tumor, the tissue is collected and placed in a separate specimen container than that used for the rest of the procedure. These last specimens may be discarded. The base of the crater is then completely fulgurated. Expressed in another way, if sufficiently small to be resected with ease, the lesion and a cuff of normal bladder are removed.

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[7] Foley, F. E. B.: In discussion at meeting of North Central Section, Minneapolis, Minn., October 1952.

Tumors larger than those just described are truly biopsied, in that deep tissue pieces are removed only at several areas of the base and periphery.

INTERPRETATION OF SPECIMENS

All pathology specimens should be examined microscopically by the urologist, or in lieu of this, by a pathologist. The following questions require an answer:

a) Does the tumor invade only mucosa and submucosa?

b) Are only the mucosa, submucosa and very superficial muscle bundles involved?

c) If the tumor involves very superficial muscle layers only, is there a very generous area of uninvolved muscle beneath the tumor cells?

d) Does the tumor invade the deeper parts of the muscle in any of the tissues?

e) Does any of the normal bladder cuff, excised from around the tumor, contain tumor cells?

TREATMENT DEPENDING ON PATHOLOGICAL FINDINGS

If only mucosa or mucosa and submucosa contain cancer, then there is probably no vesical lymphatic spread. If the bladder surrounding the lesion is free of tumor cells, then apparently no further therapy is necessary. If sections of the bladder surrounding the lesion reveal cancer cells, a wider transurethral resection or segmental resection is indicated.

If only very superficial muscle bundles are invaded, then it appears that about 50 per cent will have some degree of local vesical lymphatic spread of tumor cells. If muscle sections from the bladder surrounding the lesion are free of cancer cells, then possibly no additional surgery is indicated.

If the bladder muscle about the tumor contains malignant cells, a more extensive transurethral resection is indicated, but generous segmental resection or hemicystectomy would appear more certain to completely excise the tumor. Apparently lymphadenectomy is not indicated.

The present investigation indicates that if the tumor extends deeply into the bladder but less than 50 per cent of the muscle wall is infiltrated, then about half of the cases will not have extensive local vesical lymphatic tumor dissemination. The remainder may not only have moderately extensive circumferential lymphatic spread within the bladder, but it is possible to have tumor cells in regional lymph nodes. Concerning additional therapy for all patients of this group, cystectomy is probably unnecessary while classical segmental resection or further transurethral resection is undoubtedly inadequate treatment. While certain urologists may prefer total cystectomy and lymphadenectomy, it is highly probable that hemicystectomy and lymphadenectomy is a procedure that should completely excise the cancer in most of these patients.

Tumors that have infiltrated considerably more than 50 per cent through the muscle should be treated either palliatively or by total cystectomy and lymphadenectomy depending on experience or conviction of the urologist. Regardless of attitude or method of treatment, the data indicate that the prognosis is poor for this large group of patients.

There are two principal objections to the conclusions presented: First, the rate of tumor growth varies from patient to patient. It is obvious that certain highly anaplastic, rapidly growing cancers may have greater circumferential lymphatic dissemination than slower growing tumors of the same depth of infiltration. Second, only 18 bladder specimens were studied in this series. Due to this small sample it would be unwise to form definitive conclusions. The results do indicate, however, that an approximate correlation does exist between depth of infiltration and circumferential vesical lymphatic spread of bladder cancer. A larger series will be reported later.

CONCLUSIONS

It may be concluded from this study that it is not possible to state dogmatically the precise extent of circumferential lymphatic spread of vesical cancer by either mucosal size or depth of infiltration of the lesion. This may be determined only by careful transurethral biopsy as indicated above.

Regardless of depth of infiltration, microscopically there is exceedingly little *mucosal* spread of tumor cells other than that observed endoscopically. Local and distant lymphatic spread within the bladder is usually confined to the muscularis. In the sections studied, mucosal and submucosal cancers did not spread to adjacent local vesical or regional lymphatics. Transurethral resection and fulguration is undoubtedly the procedure of choice for this type tumor. A small percentage of cancers invading only superficial muscle fibers may have local lymphatic involvement greater than the tumor base. As a general therapeutic procedure which should cover all patients of this group, generous segmental resection should probably be performed to achieve maximum cure rate. No patients of this group had metastases to regional pelvic lymph nodes. Lymphadenectomy is probably unnecessary. Although tumors infiltrating approximately less than 50 per cent of the muscularis do not generally have extensive local vesical lymphatic dissemination, a few will have considerable circumferential bladder involvement and an occasional case will have cancer in regional pelvic lymph nodes. Transurethral resection or segmental resection as routinely performed would be inadequate therapy for these patients. Hemicystectomy and lymphadenectomy or cystectomy and lymphadenectomy would probably increase the present cure rate for this tumor group. It is of interest that a small percentage of tumors that have infiltrated half way or more through the muscularis failed not only to have metastases to regional pelvic lymph nodes, but also did not spread for any considerable degree to adjacent lymphatics within the bladder wall. Usually, however, neither of these conditions obtained for this group of infiltrative cancers. Tumor cells usually involved 60 per cent or more of the circumference of the bladder and there were tumor bearing lymph nodes in about 80 per cent of cases.

Intelligent use of transurethral resection biopsy of the malignant lesion and the surrounding "normal" bladder would probably afford nearly the same information concerning circumferential lymphatic spread of cancer cells as total coronal sections of the bladder.

The advantages and disadvantages of transurethral or the routine segmental resection are discussed. The rationale for hemicystectomy in conjunction with lymphadenectomy is presented.

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MALIGNANT HEMANGIO-ENDOTHELIOMA OF THE URETHRA: A CASE REPORT

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Primary malignant tumors of the urethra are rare Except for a few sarcomas, the majority of reported cases have been squamous cell and transitional cell carcinomas However, Rolnick, in 1940, collected from the literature a group of 50 cases of sarcoma of the penis in which were included 12 instances of malignant endothelioma In 1946, Coppridge et al reviewed these latter cases of malignant endothelioma and presented an additional one of their own The recent report of Cornwall and Whitaker in 1953 brings the known recorded total to 14 In all of these cases the tumor originated in the corpora and invaded the urethra only secondarily This paper describes the first known case of malignant endothelioma presenting as a tumor of the urethra A discussion of the classification and histopathology of this rare neoplasm is presented

CASE REPORT

A 54 year old white man was admitted on November 26, 1953 with a 3 day history of painless hematuria He denied any past history of urethral stricture, infection or instrumentation

Physical examination revealed a tender, firm nodule, 1 cm in diameter, in the floor of the anterior urethra approximately 6 cm proximal to the urethral meatus

The admission urine exhibited microscopic hematuria Otherwise the routine hematologic studies and x-rays were normal

An initial urethrogram revealed a nonopaque filling defect in the anterior urethra (fig 1) On December 1, 1953, urethroscopy disclosed a hemorrhagic, cystic tumor arising from the anterior urethral floor This was excised with the resectoscope loop and its base fulgurated The pathologist's report was simple capillary hemangioma The patient experienced an uncomplicated postoperative course and was discharged from the hospital on December 4, 1953

He returned on February 1, 1954 complaining of intermittent urethral bleeding of 3 weeks' duration and an aching discomfort in the left hip Examination revealed a discrete, tender nodule, 0 5 cm in diameter, at the approximate site of the original tumor

Cystoscopy was performed on February 5, 1954 and a discrete nodule was observed arising from the right wall of the anterior urethra approximately 6 cm proximal to the external urethral meatus This was resected and the base thoroughly fulgurated

Microscopic examination of the surgical specimen showed irregular spaces lined by relatively large, irregular, polygonal to umbrella shaped cells which possessed a moderate amount of amphoteric cytoplasm, moderately distinct

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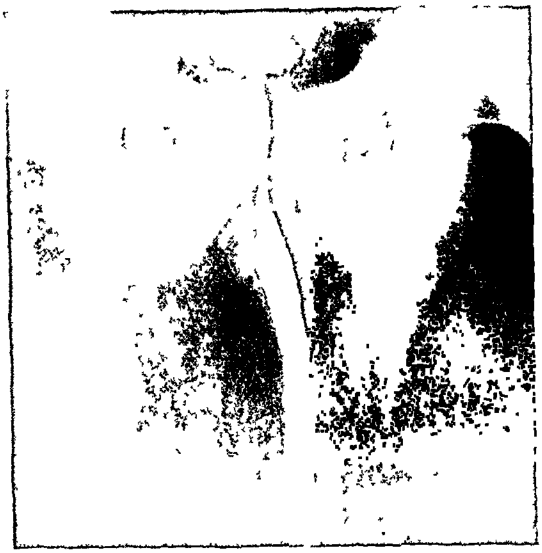

FIG. 1. Urethrogram showing filling defect in distal portion of the anterior urethra.

cytoplasmic borders and large vesicular to hyperchromatic basophilic nuclei. A few round eosinophilic nucleoli were seen. No mitotic figures were noted. Many of the spaces contained erythrocytes. The ramifying and interlacing septae between these spaces consisted of fibroblasts and smooth muscle cells. Comparison with the first biopsy specimen was made and the original tumor was noted to possess septae of uniform thickness and only a suggestion of papilliform processes. The second biopsy showed more pleomorphism of the living cells, and within some of the septae there were sheets and masses of the lining cells (fig. 2). The pathological diagnosis was hemangioendotheliosarcoma of the urethra (Dr. William Morningstar).

At this point radical amputation of the penis was considered. As the patient continued to complain of pain in the region of the left hip, making walking uncomfortable, a film of the pelvis was obtained on March 9, 1954. A circular area of destruction was noted involving the superior ramus of the left ischium and invading the hip joint (fig. 3, *A*). A previous film of the pelvis made at the time of the original admission had been interpreted as being negative (fig. 3, *B*). Biopsy of the bony lesion was performed on March 15, 1954. The cortex of the ischium was destroyed over its posterior surface and there was invasion of the soft tissues adjacent to this area. Microscopic sections revealed similar structures and cells as noted in the urethral biopsies. In the bone there was a moderate desmoplastic reaction and osseous proliferation about the periphery of the tumor mass. Also, the solid collections of tumor cells were larger, with a degree of pleomorphism comparable to the second urethral biopsy (fig. 4).

A skeletal survey was negative for other metastatic foci. The patient was started on irradiation therapy to the left ischium on March 22, 1954. A total tumor dose of 3500 r was given, interrupted only by the discovery and drainage of a left gluteal abscess on April 15, 1954.

On September 1, 1954 the patient was walking and free of pain. He had no uri-

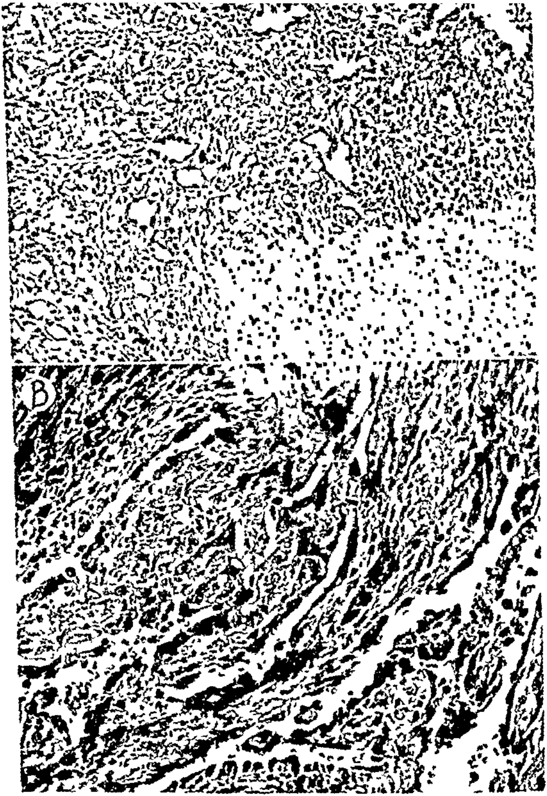

Fig 2. *A*, photomicrograph of removed tumor displaying numerous well-defined vascular spaces surrounded by an anaplastic stroma. *B*, selected focus in same specimen depicting anastomosing capillaries lined by swollen endothelial cells

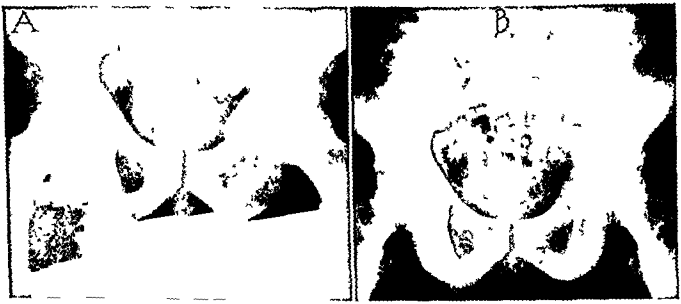

Fig 3 *A*, plain film of the pelvis exhibiting an osteolytic lesion destroying superior ramus of left ischium *B*, admission film of pelvis which was interpreted as normal

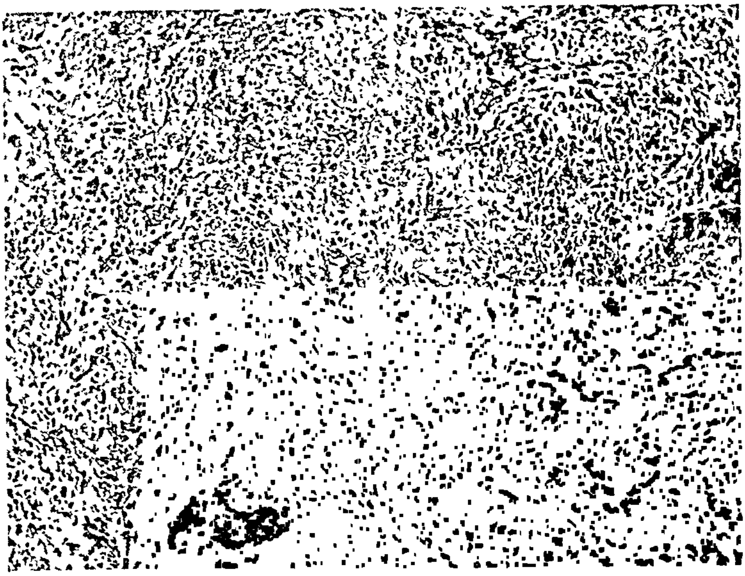

Fig. 4. Photomicrograph of biopsy taken from left ischium showing a marked similarity to figure 2, *A*.

nary symptoms, and the penis was grossly normal. Urethroscopy repeated on two occasions revealed no evidence of recurrent urethral tumor. Cysto-urethroscopy on January 4, 1955 disclosed a normal urethra. X-ray films of the area of metastasis exhibited definite sclerosis. A skeletal survey was negative and the patient asymptomatic.

DISCUSSION

The general state of confusion that exists today in regard to the descriptive terminology and pathological classification of malignant tumors of blood vessel origin is quite remarkable. The only agreement appears to be one of disagreement.

There are a few authorities that doubt the origin of malignant tumors from endothelium. However, gradually a body of knowledge has been accumulated that lends itself to classification. Stout has pioneered in the microscopic study and pathological grouping of the angiosarcomas and has proposed the following classification:

1) Malignant hemangio-endothelioma (synonyms: angiofibrosarcoma; hemangioblastoma; hemangio-endothelioblastoma; hemangio-endotheliosarcoma).

This tumor apparently arises from vascular endothelium and is characterized microscopically by congeries of atypical capillaries with a marked tendency to frequent anastomosis, and lined by swollen, anaplastic endothelioblasts that partially fill the lumens. In addition, the tumor cells are confined within a delicate reticulin sheath surrounding each vessel which serves to distingiush it from that group referred to as—

2) Malignant hemangiopericytoma (synomyms: angiosarcoma; hemangio-endothelioma; hemangiopericytic sarcoma; perithelial angiosarcoma; perithelioma).

In this tumor the blood vessels are lined by normal endothelium and the tumor cells are clustered outside of but closely applied to the reticulin sheath. The dominant cell is the pericyte and is readily observed in its benign form, the glomus tumor

3) Kaposi's sarcoma (synonyms angiosarcoma multiplex, multiple idiopathic hemorrhagic sarcoma, sarcoma cutaneum telangiectaticum multiplex, etc)

The microscopic picture is one of interlacing groups of capillaries associated with growth of spindle shaped cells and connective tissue fibers suggestive of fibrosarcoma

4) Lymphangiosarcoma

This is a malignant tumor thought to arise from lymphatic endothelium

Of prime concern to the urologist is the malignant hemangio endothelioma which, in Stout's opinion, embraces those malignant endotheliomas arising from the vascular endothelium within the corpora cavernosa and heretofore reported as presenting as a penile tumor

The tumor in our case, as can best be determined, arose from blood vessel endothelium in the corpora spongiosum and grew into the penile urethra with resultant ulceration and hematuria It qualifies as a hemangio endotheliosarcoma or under the classification proposed by Stout, a malignant hemangio endothelioma To the best of our knowledge it represents the first such tumor presenting in the urethra

Kaposi's sarcoma has been described originating on the glans penis and must be considered in the differential diagnosis of hemangiosarcomas of the penis

Benign angiomas of the glans penis and anterior urethra have been reported However, in none of these cases did progression to a malignant state occur This factor brings up several interesting points concerning the pathogenesis of malignant hemangio endotheliomas The first concerns the hypothesis of trauma and secondary production of granulation tissue with its rich capillary network and subsequent progression and development of a malignant hemangio endothelioma This has given rise to the term, granulation tissue sarcoma It is very possible that our case can be explained on this basis as it was first considered a simple capillary hemangioma and following electrofulguration developed malignant changes with progression to hemangiosarcoma

McCarthy and Pack, reporting on a series of 20 cases of angiosarcoma occurring in various sites, included three instances of angiosarcoma developing from benign angioma previously controlled by irradiation therapy with apparent cure, in 1 case, extending as long as 15 years

Secondly, we are concerned with the proposed entity of benign metastasizing hemangioma in which the original tumor is a benign hemangioma with subsequent appearance in distant areas as hemangioma or malignant hemangio endothelioma A number of such cases have been reported and, in one or two instances, apparently confirmed However, the majority are thought to be originally malignant and the entity, as such, is rather dubious

Microscopically, angiosarcoma may be confused with chorio epithelioma and the metastatic lesions of clear cell carcinoma with the latter tumor, perhaps, accounting for a certain number of erroneously diagnosed cases of angiosarcoma of bone

The proper therapy in these cases is based upon the location and gross extent of the tumor. Metastases usually occur via the blood stream. However, lymphatic spread is not uncommon and, although relatively slow, may on occasion be extremely rapid, as demonstrated by our case in which marked metastatic destruction of bone occurred 3 months following previously negative radiographic findings. The treatment of choice is therefore radical excision or amputation with irradiation and radium therapy reserved for advanced or inoperable cases.

The reported average survival period of malignant hemangio-endothelioma varies from 1 to 2½ years, compared to 8 years for Kaposi's sarcoma.

SUMMARY AND CONCLUSIONS

A case of malignant hemangio-endothelioma, apparently arising from the corpus spongiosum, but presenting as and exhibiting the clinical characteristics of a urethral tumor, is described as the first of its type recorded.

The pathological classification and microscopic description of that group of malignant tumors of blood and lymph vessel origin, termed the angiosarcomas, are presented.

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ERYTHROPLASIA OF QUEYRAT WITH INVASIVE CARCINOMA AND WITH COINCIDENTAL CARCINOMA IN SITU OF URETHRA

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Erythroplasia of Queyrat is recognized as a precancerous lesion on the penis. Observations have shown that if the process continues unchecked, a carcinoma develops with great regularity. The condition is rare and is therefore often unrecognized. For these reasons and because the subject of this report showed the full course of the natural history of the lesion with subsequent development of carcinoma, the case was thought worthy of description. Besides, the patient had a carcinoma of the urethra, unrelated to the invasive carcinoma of the glans penis following erythroplasia of Queyrat and also had been treated for a carcinoma of the mouth. The finding of three separate carcinomas, while not a rarity, is sufficiently infrequent to be worthy of mention.

Study of the literature shows that all of the lesions of erythroplasia of Queyrat that have been kept under observation have turned into cancer. While certain writers have minimized the seriousness of erythroplasia of Queyrat, the preponderance of clinical opinion now is to view this condition with more respect. The glans penis and prepuce are usually involved but the lesion has been also reported in the mucus membrane of the mouth and vulva. Bowen in 1912 described a chronic skin condition, since called Bowen's disease, involving primarily the superficial layers of the oropharynx, genital or anal regions. The histopathology as described by him is similar to the changes in erythroplasia of Queyrat. In 1911, Queyrat had described these changes and used the term, erythroplasia of the glans.

The lesion is shiny, of a bright, cherry red color and with a clearly demarcated border. Until subsequent degeneration takes place, there is no induration. It is not painful but, when extensive, it becomes sensitive to touch. The clinical course is one of slow spread to the coronal sulcus and to the mucous membrane of the prepuce. This may take many years and affords the patient an opportunity to wander from doctor to doctor and from clinic to clinic. Recognition of the lesion by the doctor with constant observation of the patient will aid in discovering the early malignant change and instituting definitive treatment.

The diagnosis is made only by biopsy of the suspected tissue. The histologic features characteristic of this lesion are keratoses, proliferation of the epidermis and inflammatory changes in the cutis. The following conditions must be considered in the differential diagnosis: syphilis, skin changes seen in diabetes and contact dermatitis, granuloma inguinale and carcinoma of the skin. Serological tests for syphilis, complete blood count, urine analysis and dark field examination when indicated would help to differentiate these conditions.

Treatment has varied from local application of soothing ointments and

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lotions, application of radium, electrocoagulation or x-ray therapy to surgical removal of the lesion. Our present belief is that surgical removal is the only way of effecting a cure. Amputation of the penis may be sufficient but some surgeons include a radical node dissection of the groin. Few urologists would recommend such a radical treatment for a superficial lesion and it is likely that few patients would accept such a recommendation even if made. It is important that close, periodic observation of the patient be carried out.

The following case is presented for its interesting history and histologic findings. A Negro aged 59 was admitted to the Bronx Veterans Administration Hospital on September 14, 1953, complaining of an exquisitely tender glans penis. He was unable to tolerate any contact of the underclothes with the glans.

His lesion had first been noticed as a small, red spot 30 years ago. It did not bother him and seemed to be quiescent for about twenty years. In the past 10 years there had been a slow but steady growth. The prepuce had become involved and the right side was so scarred that it looked as though a circumcision had been done.

The first admission to this hospital was in 1947 for a swelling in the floor of the mouth and undersurface of the tongue. Biopsy was reported as squamous carcinoma and x-ray therapy was given with excellent results. A swelling in the right groin was also found. The diagnosis of granuloma inguinale was made although Donovan bodies were not found. The Frei test for lymphogranuloma inguinale was negative. The patient was given tartar emetic, 45 mg. twice a week and the inguinal lesion healed in 5 months.

He again returned to this hospital in August 1949 for symptoms suggestive of coronary sclerosis. Physical examination of the genitalia and inguinal region showed extensive scarring of the right groin and a deformity of the penis due to retraction of the prepuce. This retraction was caused by fibrosis centered at the coronal sulcus. Micturition was normal since the meatus was free of obstructing tissue. A course of penicillin therapy was given for his latent syphilis.

A third admission occurred in March 1952 because of pain in the glans penis. The glans was now markedly reddened and "raw." Palpation of the glans and coronal region caused much pain. The penis was deformed due to the retraction and scarring of the prepuce. Since local treatment had no effect on the lesion or the pain, the patient was advised to undergo amputation of the penis. He thereupon left the hospital.

In September 1953 the patient felt compelled to enter the hospital because he could no longer tolerate the pain in his glans penis. The lesion was bright red, irregularly circular, with a sharp border and very tender to touch. A mass of firm tissue on the right side at the coronal sulcus represented the remnant of the prepuce, which was drawn over to the right. The opening of the urethra could not be seen. The groin was scarred as before. A vaseline gauze dressing had been applied by the patient to the glans to protect it from his clothing. When we gave him a nupercainal ointment, he experienced much relief temporarily but would allow no one to apply or remove the dressing.

Laboratory studies disclosed 4,020,000 erythrocytes, 4750 leukocytes, with 45 neutrophils, 50 lymphocytes, 4 monocytes and 1 eosinophile. The hemoglobin

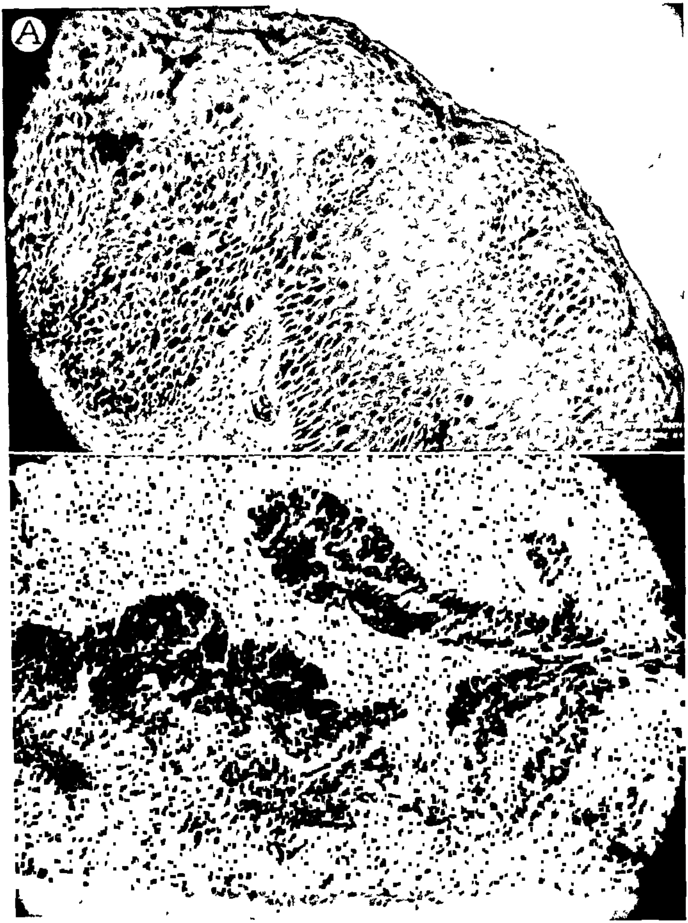

FIG. 1. *A*, from cutaneous surface of penis near the meatus. Note intra-epidermal carcinoma changes. *B*, from glans. Note bands of carcinoma beginning to infiltrate from ulcerated surface. *C*, section through urethra is normal with thickened epithelium Cracks are artificial. *D*, carcinoma in situ with numerous giant cells containing lobulated nuclei.

was 13 grams. The specific gravity of the urine was 1.022, no sugar was found but a trace of albumin was present. Microscopically 50 white blood cells per high powered field were seen. The Kolmer-Wassermann test was positive. Blood studies showed urea nitrogen 24 mg. per cent, sugar 99 mg. per cent and uric acid 4.9 mg. per cent. Acid phosphatase 0.0 Shinowara units (normal 0–1.1), alkaline phosphatase 3.6u (normal 2.2–8.6). The sedimentation rate was 31

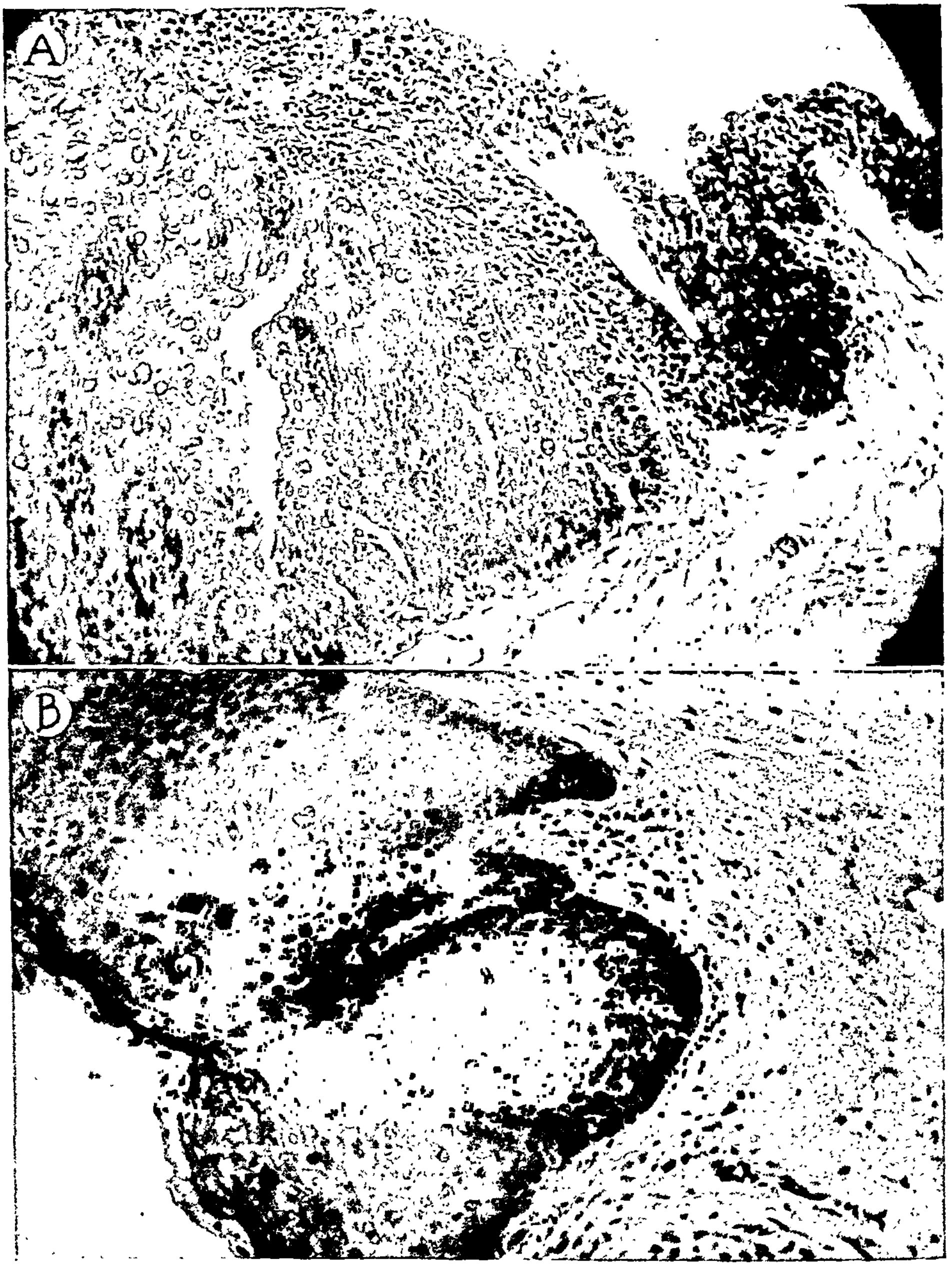

FIG. 2

mm. per hour (moderately elevated). The electrocardiogram showed changes compatible with an old, posterolateral myocardial infarction. X-ray of the chest was normal. The excretory urogram showed a few prostatic calculi. In addition, a skeletal survey disclosed no evidence of metastatic disease.

A diagnosis of erythroplasia of Queyrat was made and the patient was again advised to have his penis amputated. He now consented because the pain had become intolerable. On September 25 operation was performed. A racket incision was made about the base of the penis and dissection carried down through the fascia which was thickened and indurated. The suspensory ligament was transected and the corpora cavernosa cut across after dissecting away the corpus urethrae. The stump of the urethra was sutured and re-inforced by Buck's fascia. The urethra was then brought out through a stab wound just below the scrotum and sutured with interrupted silk sutures to the skin. The excess mucous membrane was cut away leaving a bud around an indwelling Foley catheter. Two tissue drains were removed on the third day and the wound healed by primary intention. The urethral catheter was removed on the eleventh postoperative day and he voided well thereafter in the sitting position. He left on the fourteenth postoperative day, comfortable and pleased. Subsequent examinations 1 and 3 months later have shown no tumor recurrence and the patient leads a satisfactory life.

Microscopic examination (Dr. Amour F. Liber, pathologist): See figures 1 and 2. "Sections from the cutanous surface of the shaft, corona and glans reveal multiple areas of intra-epithelial change, varying considerably from place to place. There are patches of excessive keratinization, some with parakeratosis. Many areas are characterized by proliferation and disorganization of the prickle cell and basal cell layers of the epidermis. Here, the stratification of the cells is lost and their arrangement is haphazard to varying degrees. There is marked variation in size of cells and nuclei. Many cells have lost their intercellular tenofibrils and are sometimes rounded off. Nuclei are often irregularly lobulated or multiple, with up to four or six lobes or nuclei in one cell. Many nuclei, both large or small, are markedly hyperchromatic. In the foci of proliferation, most or all of the nuclei have greatly enlarged and sometimes multiple nucleoli. Mitoses are frequent and occasionally tripolar or otherwise anomalous. Occasional cells in these areas show unicellular keratinization within the prickle cell layer. The basement membrane is sometimes irregularly wavy and occasionally indistinct. Underlying the altered areas of epidermis there often is an inflammatory infiltration of lymphocytes, plasma cells and occasional neutrophiles. Melanin pigmentation is present in varying amounts in both the normal and the proliferating epidermis and is frequently seen in macrophages in the superficial dermis. Near the meatus, there are several columns of proliferating epidermal cells invading deeply into the dermis which at this point is partially necrotic and intensely infiltrated with neutrophiles and other leukocytes.

"The urethral epithelium is patchily thickened and metamorphosed into an epidermoid layer with occasional complete keratinization. Some of the keratinized as well as some of the nonkeratinized areas present alterations similar to the proliferating patches described in the epidermis. Here, the number of cell layers is notably decreased. There is irregularity in the arrangement and size of the cells and a general hyperchromasia of the nuclei, although in most areas there is less multinuclearity of the cells and there are less nuclear irregularities than in the epidermis. Mitoses are frequent in these areas. There is no evidence of invasion. The epidermoid metaplasia and proliferation extend into some of the para-urethral gland ducts and acini; sometimes they lie side by side with normal glandular acini.

"The connective tissue structures of the dermis of the skin, corpora cavernosa, corpus spongiosum, fasciae and corium of the urethra all have undergone severe and extensive fibrosis with patches of hyalinization and hyperelastosis. Many blood vessels have markedly thickened and fibrosed walls, without predilection for one coat of the vessel wall. The smooth muscle of the dartos and erectile structures is atrophic in many areas, being replaced by fibrosis.

"The base of the excised segment is microscopically free from pathologic changes, with unaltered epidermis and urethral mucosa, as well as normal corpora cavernosa and spongiosum.

"Diagnoses: Erythroplasia of penis. Superficially invading epidermoid carcinoma of glans near meatus. Carcinoma in situ of urethra. Fibrosis of interstitial tissues of penis."

The patient was re-examined during February 1955. He was in excellent health and voiding at normal intervals. There was no evidence of recurrence of tumor or inguinal adenopathy.

DISCUSSION

A case of erythroplasia of Queyrat has been presented showing its tendency to chronicity and to malignant change over the course of years. Histologic proof of cancer in the early lesion has never been shown and it is likely that carcinoma starts in the tissue that has been involved for many years. Bowen's disease is considered to be the same condition but is found in the mouth and anal region. This too is now found to undergo malignant change in the course of many years. The lesion of the nipple, first described by Paget in 1875, is not now considered to be similar to these two, although for many years the three conditions were felt to be the same disease but found in different parts of the body.

The finding of a separate carcinoma of the urethra is interesting but multiple cancers of the genito-urinary tract have been described previously. This patient in addition had a third carcinoma of the mouth which also was successfully treated. Since he has faithfully reported for follow-up care for the past nine months, we hope to continue the study of his case.

SUMMARY

Erythroplasia of Queyrat is an intra-epidermal cancer which from its inception seems to follow a histologic course of malignant change. It must be considered in the differential diagnosis of disease of the glans penis. In addition, we were able to find an in situ carcinoma of the urethra which appears to have no relation to the original lesion of the glans. This patient was operated on, the penis removed and he has been well to the time of this report, 9 months later.

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A NEW PROSTATIC FISTULA

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In 1939 Huggins et al.[1] described the preparation of a prostatic fistula in dogs which permitted periodic collection of prostatic and urethral secretions over considerable periods of time under the stimulus of parasympathomimetic drugs. Fistulas were described previously by Eckhard[2] and Farrell,[3] but Huggins found the procedure of Farrell to be technically unsound for four reasons: "There was a high mortality rate; the skin constantly bathed in urine became macerated and ulcerated; the perineal fistula had a tendency to close, and quantitative collections through it were difficult."

As described in 1939, the Huggins' fistula was prepared by transecting the neck of the urinary bladder as close to the prostate as possible, closing both of the cut ends with separate sutures, diversion of the urine with a metal cannula and circumcision, the latter done to permit an Erlenmeyer flask used for collection of fluid to be slipped over the penis and held in place with a cloth sling (fig. 1).

During the course of some 13 years, Huggins and his associates have made many efforts to improve this procedure. In their most recent paper[4] they report that three modifications have proved useful: "1) A light metallic cannula of wide bore is now used to replace the original, heavy, narrower brass tube, with consequently an important decrease in infection of the urinary tract, promoting better health of the dogs. 2) The apparatus for collecting prostatic fluid has been improved (fig. 2). 3) The utility of the investigative method has been increased in another way by use of the prostatic translocation operation (fig. 3 . . ." In this procedure the prostate is transplanted into the perineum after division of all its attachments except those to the urethra distal to the prostate. However, a permanent, indwelling, metallic cannula is still used for urinary drainage. The advantages claimed for this modification are: 1) It permits the size of the prostate to be measured. 2) Pure prostatic fluid unmixed with other secretions is obtained. 3) Prostatic secretion can be collected and measured continuously as it is produced instead of being released intermittently in spurts by the external urinary sphincter.

We, too, have labored to improve the original Huggins' fistula, believing that the chief disadvantage of such, as well as recent modifications, is renal infection, leading to early uremia and death within a few months.

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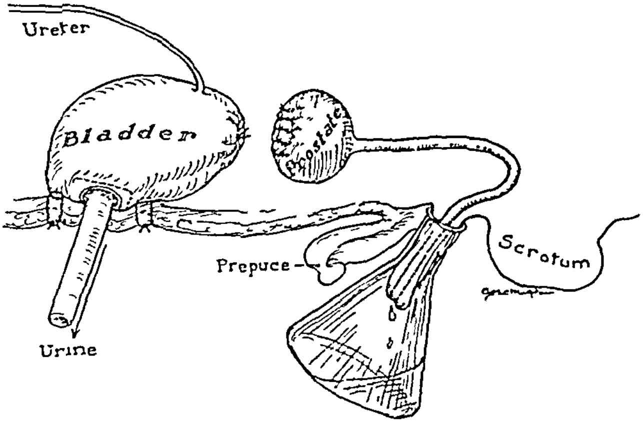

FIG. 1. Prostatic isolation operation as described by Huggins, et al. (J. Exp. Med., **70**: 543, 1939). Courtesy of Dr. Charles Huggins.

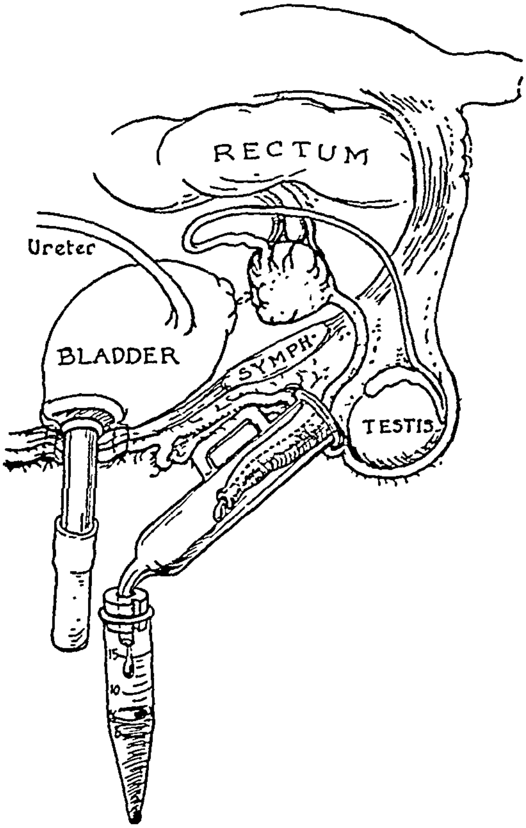

FIG. 2. Improvement in method of collecting prostatic fluid as described by Huggins and Sommer (J. Exp. Med., **97**: 663, 1953). Courtesy of Dr. Charles Huggins.

It became clear early in our experience that diversion of the urine by ureterointestinal anastomosis was not the answer because of the high incidence of renal infection and failure, as well as electrolyte imbalances, attendant to such.

We, therefore, developed a method of preparing a prostatic fistula in the dog which permits collection of pure prostatic secretion without disturbance of

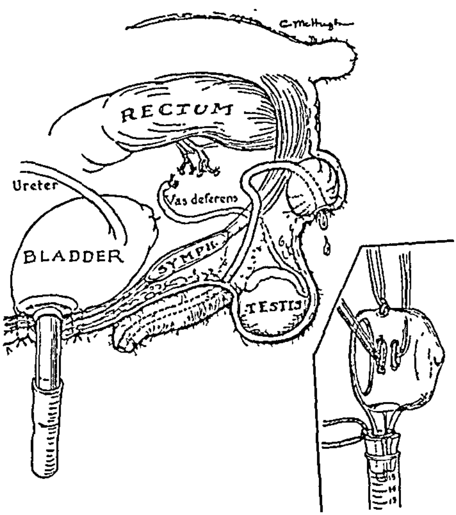

Fig. 3. Prostatic translocation operation as devised and illustrated by Huggins and Sommer (J. Exp. Med., 97: 663, 1953). Courtesy of Dr. Charles Huggins.

normal micturition. The method of preparation and the results experienced in the first 11 dogs follow:

METHODS

All operations were performed on dogs under sodium pentothal anesthesia and using aseptic technique. The abdomen was opened through a left pararectus incision, the lower limb of which extended to the pubis, and the bladder delivered. The prostate gland (intraperitoneal in the dog), vesical neck and urethra down to the urogenital diaphragm were freed anteriorly and laterally. Dissection was then carried around the entire circumference of the vesical neck which was then divided over a clamp, leaving a cuff of bladder wall anteriorly but taking care posteriorly to preserve the ureteral orifices and vesical blood supply. As described in an earlier communication from this laboratory[5] the blood supply of the bladder and prostate gland of the dog arises from a common pedicle on each side but separate at sufficient distance from these organs to allow them considerable independent mobility (fig. 4). These pedicles also contain nerves. The vasa deferentia were divided (there is reason to believe this is not mandatory) and the prostate gland freed posteriorly between the right and left vascular-nervous pedicles. The apex of the prostate and the adjacent urethra were dissected free around their entire circumference and the urethra divided immediately distal to the prostate but proximal to the external urethral sphincter.

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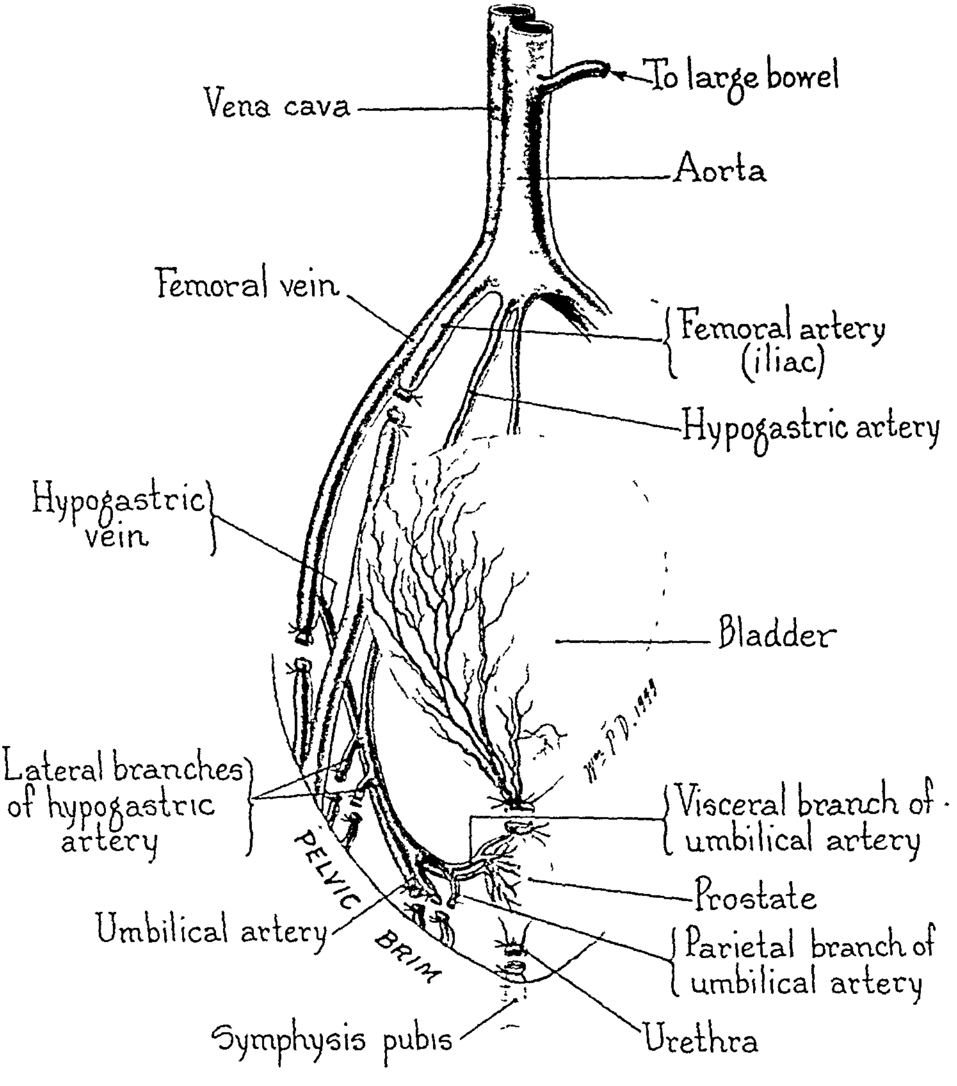

FIG. 4. Blood supply of prostate gland of dog as illustrated in earlier communication from this laboratory (J. Urol., 63: 319, 1950).

The prostate gland was thus entirely freed of its attachments except for its vascular-nervous pedicles. Next, the neck of the bladder was brought down posterior to the prostate gland between the right and left pedicles and sutured to the cut end of the urethra over a splinting 12F catheter using four everting mattress sutures at 3, 6, 9 and 12 o'clock. After fixation of the bladder wall to the anterior abdominal wall, the bladder was closed around a temporary rubber cystostomy tube inserted near the fundus of the bladder and brought out through a stab wound lateral to the main incision. The distal end of the prostatic urethra was then closed and the gland swung subcutaneously into the angle of the abdominal incision and secured to the anterior rectus sheath and subcutaneous

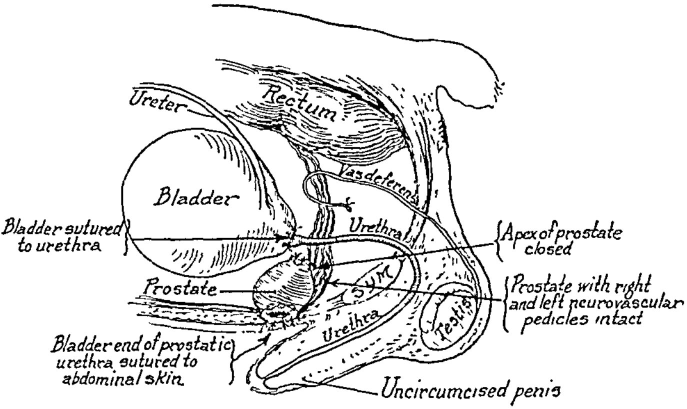
Rectum
Ureter
Bladder
Vas deferens
Urethra
Bladder sutured to urethra
Apex of prostate closed
Prostate
SYM
Prostate with right and left neurovascular pedicles intact
Testis
Urethra
Bladder end of prostatic urethra sutured to abdominal skin
Uncircumcised penis

FIG. 5. New method of preparing prostatic fistula which permits collection of pure prostatic secretion without disturbance of normal micturition.

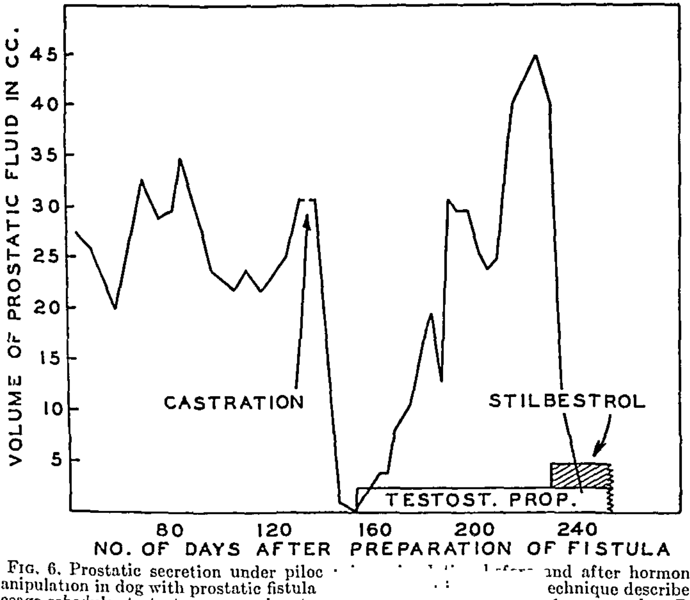

FIG. 6. Prostatic secretion under piloc [illegible] and after hormonal manipulation in dog with prostatic fistula [illegible] echnique described. Dosage schedule: testosterone propionate, [illegible] 1 mg. per day. Response is identical to that observed by Huggins, et al.[1] using his original fistula.

fascia without division of or embarrassment to the pedicles. The epithelium of the prostatic urethra was then joined with the adjacent skin of the abdomen by interrupted sutures and the abdominal wound closed in layers after a Penrose drain had been placed to the site of the anastomosis. The Penrose drain was left in place for 48 hours, the urethral catheter for 1 week and the cystostomy tube for 3 weeks.

Figure 5 is an illustration of this procedure.

RESULTS

Eleven prostatic fistulas have been prepared according to this new method. Two animals have died. The first death occurred 1 week after operation and appeared to have resulted from urinary extravasation. This was the first attempt and no cystostomy tube was used. The second occurred 3 months after operation, and at autopsy it was not possible to determine the cause. The urinary tract was normal except for a small calcareous deposit at the site of the previous cystostomy. The vesico-urethral anastomosis was well healed and widely patent.

The remaining 9 animals are alive and well for periods ranging from 3 to 11 months. All are continent of urine and have been observed to void with a urinary stream of good force and caliber. All have produced substantial amounts of prostatic fluid on stimulation with pilocarpine ranging to 45 ml. for one collection. This fluid has been collected by means of a wide-mouthed funnel and container fastened loosely over the external opening of the fistula. It appears to be clearer than fluid obtained with the original Huggins' fistula, presumably because it is not contaminated with urethral secretions. Fistulas have remained open without manipulation in eight. In one, surgical revision was necessary to correct a stricture at the external opening. A sample record of prostatic secretions of one of the animals is shown in the chart depicted in figure 6.

SUMMARY

A new method of preparing a prostatic fistula in the dog is described which permits prostatic fluid to be collected without disturbing urinary function. Nine of 11 dogs so prepared have functioning fistulas 3 to 11 months after operation. All of these have responded characteristically to pilocarpine stimulation and hormonal manipulation.

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THE INCIDENCE AND TYPE OF BACTEREMIA AT THE TIME OF VARIOUS PROSTATECTOMY PROCEDURES

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The literature gives convincing evidence of the common occurrence of bacteremia and septicemia following the manipulation of the prostate and male urethra prior to the advent of the antibiotics and the chemotherapeutic agents. Scott in 1929 studied 82 patients with bacteremia or septicemia following such procedures as perineal prostatectomy, cystoscopy, urethral dilatation, and the insertion and removal of catheters and packs. In this group there was a mortality of 18.0 per cent. Barrington and Wright showed in 1930 that bacteremia occurred a few minutes to a few hours after urination in a high percentage of patients who had received urethral dilatations. This indicates the prevalence and seriousness of bacteremia and septicemia in the common urological procedures before the advent of the antibiotics and the chemotherapeutic agents.

Creevy and Feeney have shown that in patients receiving no antibiotics or chemotherapeutic agents 45.7 per cent had positive blood cultures at the end of transurethral resection of the prostate. This incidence was markedly reduced to 17.4 per cent by the use of aureomycin. Biorn, Browning, and Thompson showed in a study of 106 cases an incidence, after transurethral resection of the prostate, of 12.2 per cent positive blood cultures. No statement was made as to the use of chemotherapeutic agents.

In view of these findings a study of the incidence and type of bacteremia in patients receiving aureomycin and on whom prostatic surgery was performed was instituted in an effort to evaluate the comparative incidence following open prostatic surgery and transurethral resection of the prostate.

METHOD

The 203 cases studied in this series were consecutive prostatectomies at Strong Memorial Hospital from October 1951 to June 1953. In the 24-hour period before operation each patient received 1 gm. of aureomycin orally in two equal doses. In preparation for surgery a majority of the patients had indwelling catheters and this necessitated the use of the various other antibiotics such as gantrisin, penicillin, or streptomycin depending on the choice of the attending urologist. Aureomycin was selected for use because the work of Creevy and Feeney showed that its administration resulted in the lowest percentage of positive blood cultures following transurethral resection of the prostate. Immediately at the end of the operation the blood culture was obtained. Three cubic centimeters of blood were placed in citrate solution for the use of making blood plates and two cubic centimeters placed directly into the

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Read at meeting of Clinical Society of Genito Urinary Surgeons, Strong Memorial Hospital, Rochester, N. Y., February 5–6, 1953.

TABLE 1. *Incidence of bacteremia with various types of prostatectomy*

Type of Surgery	Number of Cases	Number Positive Cultures	Positive Cultures in Per Cent
Suprapubic prostatectomy	124	35	20.2
Retropubic prostatectomy	7	0	0.0
Perineal prostatectomy	6	0	0.0
	—	—	—
Open prostatectomy	137	35	18:2
Transurethral resection of the prostate	66	36	54.5
Totals	203	71	34.9

broth. In reading the results no consideration was made as to possible contamination.

RESULTS

The results obtained in this study are shown in table 1 which gives the number of cases studied according to the type of surgery, the number of positive blood cultures, and the percentage of positive blood cultures. There were 124 cases of suprapubic prostatectomy in which 35 had positive blood cultures or 20.2 per cent. In the next group there were 7 retropubic prostatectomies and 6 perineal prostatectomies in which there were no positive blood cultures. The total of 137 open prostatectomies had 35 positive blood cultures or 18.2 per cent. In the last group there were 66 cases of transurethral resection of the prostate in which 36 had positive blood cultures or 54.5 per cent.

The type of bacteria cultured at the time of prostatectomy varied a great deal with the character of surgery employed as shown in table 2. There was also a great variance with each particular group. With transurethral resection of the prostate 15 of the positive cultures were B. alkaligenes, 11 B. pyocyaneus, 1 B. proteus, and 3 Esch. coli and the remaining 8 divided among the staphylococci, the streptococci and the diphtheroids. With the suprapubic prostatectomy 18 of the positive blood cultures were staphylococci, 6 streptococci, 4 diphtheroid, 3 B. pyocyaneus, and 5 B. aerogenes. There were no positive blood cultures with the retropubic and perineal prostatectomies but the number of cases in each of these was small.

TABLE 2. *Types of infection with various types of prostatectomy*

Type of Surgery	Alkaligenes	Pyo cyaneus	Aero genes	Proteus	Esch coli	Staph.	Strep	Diphtheroids	Total
Transurethral resection of the prostate	15	11	0	1	3	3	3	2	38
Suprapubic prostatectomy	0	3	5	0	2	18	6	4	38
Retropubic prostatectomy	0	0	0	0	0	0	0	0	0
Perineal prostatectomy	0	0	0	0	0	0	0	0	0

DISCUSSION

There is a marked difference in the type of bacteria found in the positive blood cultures in the various types of prostatectomy procedures In the group of patients having transurethral resection of the prostate, 30 of the 38 positive blood cultures were of the gram-negative bacillary type However, in the group of patients having suprapubic prostatectomies, 24 of the 38 positive blood cultures were of the gram-positive coccal type and 4 were of the diphtheroid class Even if we throw out as probable contaminants the coccal and diphtheroid cultures, a considerable number of bacillary cultures remain as true cases of transient bacteremia This leaves us with the very interesting information that with transurethral resection of the prostate covered by aureomycin there is a 45 4 per cent incidence of positive blood cultures at the time of surgery as compared with suprapubic, retropubic, and perineal prostatectomies covered by aureomycin which showed an incidence of 5 8 per cent positive cultures

Abeshouse made the statement that the incidence of bacteremia following open prostatic surgery is considerably less than that following transurethral resection of the prostate The information presented above seems to corroborate this statement Since this study did not show an increase in mortality or morbidity in those patients having positive blood cultures, it can be assumed that the bacteremia observed was of a very transitory nature Therefore, the findings of this study do not contra indicate the use of transurethral resection of the prostate They might, however, contra-indicate the performing of other, more sterile operative procedures, such as herniorrhaphies, at the same time as prostatectomy

SUMMARY

A study of 203 patients receiving aureomycin and upon whom various types of prostatectomies were performed, has been evaluated in regard to incidence and type of bacteremia immediately following the operative procedure

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BILATERAL ADRENALECTOMY IN CARCINOMA OF THE PROSTATE

EDWARD H. RAY

Since December 6, 1952 I have done bilateral adrenalectomy on 10 patients, six with advanced carcinoma of the prostate in reactivation following periods of remission after orchiectomy which ranged from 14 months to 62 months and four with advanced carcinoma of the breast which cases were done at the request of the general surgeons whose cases they were.

In all but 1 case the operation was done in one stage using a modified lateral kidney approach. Huggins' routine of resecting the twelfth rib was followed in 5 cases but it was soon realized that this procedure was not necessary in most cases and in 5 patients the rib resection was omitted without increasing the technical difficulties of the operation appreciably. The omission of the rib resection reduces the chance of tearing the pleura and makes for a much more comfortable postoperative period with reduction of the chance of postoperative hernia. It is well to keep the incision very close to the lower border of the twelfth rib, however, so that resection can be done if needed for better exposure.

Each adrenal gland usually has one principal vein with which to be concerned. On the right that vein usually enters the vena cava at the edge of the diaphragm and on the left it usually enters the renal vein. It is very easy to tear the adrenal vein out of the vena cava on the right.

There were no postoperative deaths in this group.

Of the 6 patients operated on because of carcinoma of the prostate, five had no evidence of osseous metastasis at the time of original diagnosis and orchiectomy with institution of estrogen therapy. The sixth had orchiectomy done elsewhere and was not seen by me until just prior to adrenalectomy 14 months later.

One of the five, followed from the beginning of treatment, had marked elevation of his serum acid phosphatase at the time of orchiectomy, two had normal serum acid phosphatase levels and in two there is no record that an estimation was made.

In all five castration and estrogen therapy were followed by regressive change in the carcinoma, which was dramatic in one, good but not complete in two and only fair in two.

At the time of adrenalectomy all of the 6 patients showed extensive metastasis, to bone in five and to lymphatics only in one, with recurrence of bladder neck obstruction in only 1 case. There was marked elevation of serum acid phosphatase in one and no elevation in the other three.

Following adrenalectomy one patient whose serum acid phosphatase had been high prior to operation showed a marked and early drop in the phosphatase

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A detailed account is available in the Transactions of the Southeastern Section, 1954, pp. 107–114.

level with a return to normal in less than three months. This is the patient who showed greatest improvement and in fact the only one to date who has shown marked objective as well as subjective improvement. The other patient, whose serum acid phosphatase had been high prior to adrenalectomy, had an initial drop after adrenalectomy from 40 K-A units to 10 K-A units 32 days later, only to show a very marked rise again in three months to 79 K-A units with an associated worsening of the clinical picture. After adrenalectomy there was no change in the serum acid phosphatase levels in those patients in whom it had been normal prior to the operation.

All but one of these patients experienced relief from pain almost immediately after adrenalectomy, varying in degree from moderate to complete and lasting from only a few weeks in 1 to 14 months in another. Two showed no objective evidence whatever of improvement following adrenalectomy although one of these had made a very dramatic response to orchiectomy. In four there was objective evidence of regression present in some degree as determined by reduction in the size of the carcinomatous prostate or, as in the case of one, by reduction in the size of enlarged abdominal lymph nodes. In only one was the improvement comparable to that which sometimes follows castration, with dramatic restoration to health and vigor, but unfortunately this patient died in a distant town 14 months after adrenalectomy, apparently the result of adrenal insufficiency.

Altogether, three of these patients have died since operation: one, 14 months later; one, 5 months later; one, 8 months later.

One patient is living 2½ months after operation, in good nutritional state, with some regression of the carcinomatous prostate but still having some pain. Another is living 5½ months after operation, completely asymptomatic and able to do a full day's work on the farm but with only slight regression of his carcinomatous prostate. A third, last seen 5 months after adrenalectomy, and who had initial relief from pain of 4 to 6 weeks' duration, showed an increase in the size of his prostate with considerable increase in the pain from skeletal metastases.

DISCUSSION

I think it has been established that elimination of adrenocortical function in patients whose prostatic carcinomas have become re-activated after a period of remission induced by castration and estrogen therapy will result in a second period of remission for some and marked relief from pain in most. This second period of remission with regression of the tumor will not occur as frequently as that which occurs primarily following orchiectomy nor does it seem likely to be as enduring.

It is well known that the administration of cortisone results in a suppression of endogenous adrenocortical secretion with a decreased output of urinary 17-ketosteroids and that the withdrawal of cortisone may be followed by evidence of adrenal insufficiency. There have been a number of reports in the literature recently of postoperative deaths due to unsuspected adrenal insufficiency in patients who some time prior to surgery have taken courses of cortisone for one reason or another. Autopsy findings revealed almost complete destruction of the adrenal cortex in some of these cases.

Valk and others have suggested that cortisone may be used through its suppressing effect on adrenocortical function to achieve what might be termed a nonsurgical adrenalectomy. These authors report the results of the clinical application of this therapeutic regimen to several patients with re-activated prostatic carcinoma following orchiectomy and observed clinical improvement denoted by relief from pain, improvement in strength and reduction of serum acid phosphatase. Undesirable effects were observed, such as difficult to control sodium retention and edema, and depletion of cellular and serum potassium which required careful replacement with 2 to 3 gm. of potassium chloride daily.

If further clinical experience proves that the use of cortisone, or other adrenocortical steroids, can be relied upon to effect total suppression of adrenocortical function without more serious undesirable accompanying effects than those which follow adrenalectomy, then a welcome therapeutic replacement for adrenalectomy will have been found. Certainly the results of adrenalectomy are too meager to engender any great degree of enthusiasm and the procedure is justifiable only as a last ditch fight in a gradually losing battle for each individual patient.

Nevertheless, the operation is not nearly so formidable a procedure as I had thought, either from the standpoint of the surgeon or of the patient, and in my experience there has been no great difficulty after operation in maintaining a satisfactory electrolyte balance. This would appear to be in contrast with the experience of Valk and Owens in their use of cortisone and estrogen as a substitute for adrenalectomy.

Pearson et al. mention Graham's studies at Memorial Hospital where 32 per cent of 100 consecutive autopsies were shown to have accessory adrenal glandular masses in the celiac plexus. It would seem, therefore, that in many instances bilateral adrenalectomy actually does not constitute total adrenalectomy but since all of these patients after operation are maintained on cortisone, and supplementary estrogen is usually given, it would seem reasonable to suppose that any cortical function present in such accessory adrenal tissue would be suppressed. It should be kept in mind, however, that in some instances failure to obtain a clinical response from adrenalectomy may be due to cortical activity in larger than usual accessory adrenal masses which has not been suppressed by the maintenance dose of cortisone.

Anything more than a superficial study of the very complex endocrine relations that exist in connection with the development and growth of certain cancers, and of the vast accumulation of data resulting from the researches of almost innumerable investigators, inevitably raises more questions than are answered and tends to fill one, who is only a clinical urologist, with despair of ever being able to understand it all.

Some of the questions which have occurred to me are as follows:

1) Why should one man whose prostatic carcinoma has exhibited a fulminating

progressiveness with rapid dissemination respond so dramatically to orchiectomy alone and continue without evidence of re-activation for as long as ten years and another have re-activation within a year or two? What peculiar set of biological circumstances could account for the failure of the adrenal cortex to respond with a compensatory increase in function on the one hand and not on the other?

2) Why in some patients, after excellent regression from castration and estrogen therapy has endured for several years, will osseous metastasis occur and progress rapidly without evidence of reactivation in the prostate itself? And why after regression following orchiectomy with marked clinical improvement and evidence of healing of osteoblastic lesions would osteolytic metastases suddenly appear and be accompanied by a rapid decline of the patient?

3) Why, after all, should one carcinoma of the prostate be "androgen dependent" and another similar one appear to be "androgen independent?" Is it possible that the growth of prostatic carcinoma depends upon the presence of other hormones either alone or in certain combinations with androgen? Does the somatotropic growth hormone play any part in the production of or activity of prostatic carcinoma?

4) What happens to the production of gonadotrophic hormones when, with increasing age, there is a reduction in the production of androgen by the testes? Without the full inhibiting effect of the "feed-back mechanism" do the gonadotrophic hormones in some men continue to be produced in normal or greater amounts so that there is an excess in the blood stream and, if so, could it be possible that they themselves have an effect on the target cells of the end-organ, which in this case is the prostate?

5) If carcinomas of the prostate are androgen dependent why should most of them occur at a time in life when testicular function is diminishing and why in the case of younger men with carcinoma of the prostate should response to endocrine therapy be so generally poor?

6) In the case of orchiectomized and adrenalectomized patients whose prostatic carcinomas are susceptible to stimulation by androgen may it not be that such stimulation is received from the androgen produced by the intermediary metabolism of administered cortisone? It would seem that such an effect would be even more likely with the use of such large doses of cortisone as advocated by Valk and Owens for the complete suppression of adrenocortical function It has been shown that there is a considerable rise in the urinary excretion of 17-ketosteroids with the administration of 300 mg of cortisone daily and that this rise is greater with the use of hydrocortisone than with cortisone

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LEIOMYOSARCOMA OF PROSTATE

RUDOLPH BELL AND ROY F. STINSON, JR.

It is the desire of the authors to report a case of leiomyosarcoma of the prostate gland in a man 62 years of age who is living and presents no demonstrable evidence of metastases 3 years after operation.

CASE REPORT

J. C. M., a white man, 62 years of age, was admitted February 3, 1951 to Archbold Memorial Hospital in acute urinary retention. He had experienced no difficulty in voiding until 2 months ago when he began to have diminution in the size of the urinary stream and increasing difficulty in starting the urinary act. More recently he had had a desire to void but could not start the act. After two or three minutes rest or diversion he could try again and succeed in relieving himself. He had had no bleeding. The patient had always been in good health except for a gallbladder operation in 1941. His parents lived to be elderly. He had 6 children, living and well. There was nothing in family or past medical history to contribute to the present illness.

The head, heart and lungs presented no gross abnormality. The lower abdomen was distended to the umbilicus and tender over the distended area. Genitalia and lower extremities were within normal limits. On digital rectal examination a very large, soft mass the size of a large orange was felt in the prostatic area. The mass was tender and, apparently, fluctuated as if it were a cyst. On inserting a soft rubber catheter much pain was experienced in the prostatic urethra. The catheter was anchored in place. A plain x-ray revealed no evidence of calculi. Blood studies: red blood cells 4,090,000; white blood cells 7,150; hemoglobin 12.5 gm., 81 per cent. Blood, group O, Rh negative. Kahn negative. Nonprotein nitrogen 31 mg. per 100 cc. Sugar 111 mg. per 100 cc. Phenolsulfonphthalein: 42 per cent first 30 minutes, 10 per cent second 30 minutes. Acid phosphatase 13.3 B. units. Alkaline phosphatase 4.8 B. units.

A suprapubic exploration of the prostate was planned. On opening the bladder it was found to be filled with a large, soft mass which, apparently, fluctuated. On opening the mass a mushy substance of the consistency of hypernephroma was encountered and was removed piecemeal, 995 gm. of tissue being removed. Bleeding was profuse. It was necessary to use large hot packs in the prostatic bed to control the massive hemorrhage. Five blood transfusions and one unit of plasma were administered the first 24 hours.

Microscopic examination: The neoplasm consisted entirely of closely packed interlacing bundles of smooth muscle fibers. There was a scanty intermuscular stroma of connective tissue. Vascularity was not conspicuous, but an occasional small blood vessel was lined by neoplastic cells. The muscle cells were uniform in appearance. There were numerous mitoses.

Deep x-ray therapy was begun on the seventh postoperative day. A total of

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26,400 r units were administered over a period of 2 years On the eighth postoperative day, while the patient was receiving an enema, an end of the prostatic pack was noted in the rectum The pack was removed On the ninth postoperative day a urethral catheter was anchored in the urethra so as to enable the urethrorectal fistula to heal

The patient made a slow but satisfactory recovery and was discharged from the hospital on the eighteenth postoperative day He is observed at intervals for return of growth or metastases The suprapubic catheter is changed every 6 to 8 weeks

Eighteen months after operation a small lump was noted in the right breast On October 10, 1952 a simple mastectomy was done The growth was an infiltrating type, smooth, firm material just beneath the right nipple Microscopic study There was a circumscribed area of hyperplasia of connective tissue of the right breast There was no evidence of malignancy

On February 20, 1954 the patient was re admitted to the hospital for a change of catheter and a re evaluation of his condition The fistulous tract had not healed The bladder wall was markedly contracted Approximately 50 per cent of the urine passed through the urethra The general appearance of the patient was good except for some lymphedema of lower extremities

X ray of chest and bones revealed no evidence of metastases Because of the marked contracture of the bladder wall and the vast amount of deep x-ray therapy instituted, an excretory urogram was done The contrast medium appeared rapidly in each kidney and was excreted in a normal period of time There was no hydronephrosis

DISCUSSION

Leiomyosarcoma of the prostate is a rare condition It is classified as a sarcoma of the prostate, of which there are between 150 and 200 authentic published cases Most of these are in children, approximately one fourth of the cases reported being in children under 16 years of age Prince and Vest, in their review, found only 15 authentic cases of leiomyosarcoma of the prostate The prognosis is uniformly poor with any form of treatment, most patients are dead within a few months after operation

SUMMARY

A patient with leiomyosarcoma of the prostate is living and presents no evidence of metastases 3 years after operation The weight of the gland was 995 gm Although the bladder wall is markedly contracted as a result of the infection and deep x ray therapy, there is no accompanying hydronephrosis, as one might suspect

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IN VITRO FURADANTIN SENSITIVITY OF ORGANISMS ISOLATED FROM HUMAN URINARY TRACT INFECTIONS

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A preliminary study was made of the sensitivity of the micro-organisms commonly invading the urinary tract of man to furadantin. Ten different organisms, which were tested in this study, were encountered in routine urine cultures from fifty patients. In general, a high degree of sensitivity to the drug was shown.

TABLE 1. *Number of strains sensitive and resistant to furadantin*

Organism	Number of strains sensitive to furadantin	Number of strains resistant to furadantin
Aerobacter aerogenes	6	
Escherichia coli	8	1
Proteus rettgeri	2	
Proteus vulgaris	9	1
Pseudomonas aeruginosa	4	2
Alcaligenes faecalis		2
Shigella alkalescens	1	
Streptococcus faecalis	1	1
Streptococcus pyogenes		1
Micrococcus pyogenes var. aureus	10	1
Total	41	9

METHODS

Primary isolates of each of the organisms listed in table 1 were streaked onto the surface of bacto-dextrose proteose No. 3 agar plates or onto blood agar plates in the case of fastidious organisms. A tablet, containing 10 mg. of the drug, was then placed on each of the streaked plates employing the technique of Bondi et al. (1947). The plates were incubated overnight at 37°C and examined for zones of growth inhibition. Those showing growth inhibition were called sensitive and those showing no inhibition were called resistant.

RESULTS

Forty-one of the fifty freshly isolated strains, representing ten genera, were inhibited by furadantin while only nine were not. Table 1 shows the genera and species of the organisms tested and the number of strains of each that were sensitive or resistant under the conditions of this study.

Furadantin is the trade-mark name of Eaton Laboratories, Inc. for nitrofurantoin N-(5-nitro-2-furfurylidene)-1-aminohydantoin

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SUMMARY AND CONCLUSIONS

Data are presented showing the *in vitro* sensitivities of ten bacterial species to furadantin While only fifty strains were tested and no definite conclusions can be drawn from this limited study, it appears that most of these organisms were sensitive to furadantin It may be significant that in this *in vitro* study, organisms commonly resistant to most of the antibiotics, notably Proteus and Pseudomonas, were inhibited by furadantin The antibacterial spectrum of furadantin seems to be fairly broad

We wish to thank the Eaton Laboratories, Inc for supplying the sensitivity tablets used in this study

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AORTOGRAPHY IN RENAL ARTERY ANEURYSM

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Aneurysm of the main renal artery is comparatively a rare observation either clinically or at necropsy. Analysis of the reported cases, 93 in all, reveals little of diagnostic significance. Of this number, only 17 had a positive diagnosis. The remainder were diagnosed either at necropsy or too late for surgery.

This case of true aneurysm of the renal artery is presented in the belief that the methods herein pursued lead to a more exact and accurate diagnosis and show that "opacification of the ring," radiographically demonstrates unerringly the presence of a renal artery aneurysm.

The work of Mathé, Lowsley and Cannon and Barneston admirably describes and classifies aneurysms of the renal artery and Levine, in 1945, utilized laminograms to demonstrate his case.

The incidence of renal artery aneurysm is generally in the fifth to sixth decade and both sexes are equally represented. Gerard reported only 5 in 41,437 necropsies or about 1 in 8000.

The symptomatology was variably assessed as follows: pain was present 53 times, hematuria 38 times, a palpable mass 29 times and a pulsating mass with a systolic bruit 10 times. Rupture into the renal pelvis occurred in 2 cases and in 1 case the sac communicated with the aorta. In only 2 cases were bilateral aneurysms found. In 1 case the aneurysm was found to be a part of generalized peri-arteritis nodosa.

The most constant symptom is pain generally localized in the upper part of the abdomen and sometimes referred to the lumbar region on the side involved. In lesser instances, there were reflex gastric disturbances in which the patient was treated either for stomach or gallbladder disease.

Briefly, it is necessary to distinguish between true and false aneurysms. The latter is generally the result of injury to the artery in which the vessel was not completely torn or where fatal hemorrhage is prevented by the pressure of the surrounding tissues. The extravasated blood usually clots, becomes surrounded by fibrous tissue which then forms the wall of the aneurysm. In nearly all instances, these result from a subparietal injury without an external wound. True aneurysms in this region, like those in other parts of the body, are due to pathologic changes in the walls of the vessel itself. This defect is generally in the middle coat of the vessel at its bifurcation. As a rule, the true aneurysm is found close to, or even within, the hilus of the kidney and its walls may be formed by one or more coats of the vessel. In size, they may vary from that of a small pea to the size of an apple. It may be sacculated or fusiform.

The differential diagnosis is from calcified cysts of the kidney or spleen, calcified abscesses or hematoma, renal calculi, gallstones, calcified neoplasms and lymph nodes.

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To date, the x-ray findings are variously described as calcification in or near the kidney, usually circular in form and often incomplete and deficient in places. The location is generally anterior to the renal pelvis and medial to the upper third of the kidney. The pelvis and the upper calyces may be deformed. This shadow has been referred to as "wreath or ringlike." In all descriptions of this ringlike shadow attributed to the aneurysm, only one finding was constant and that was the presence of the radiolucent lumen of the vessel surrounded by more or less parallel calcified bordering lines.

In the case report which follows, this radiolucent lumen of a renal artery aneurysm was successfully filled by aortography so as to cause it to become radiopaque and demonstrate unerringly that it was part of the vascular system of the kidney.

CASE REPORT

Chart No. 4365, New York Polyclinic Hospital. A 49-year-old woman was first seen in April 1954. Her complaint was of pain in the back, primarily on the left side. On occasion this pain would radiate down to the left hip and leg. She also complained of vague gastric distress associated with gaseous eructations. X-ray examination of the spine at this time failed to disclose any changes in the osseous structures. It was incidentally noted that a circular calcific shadow was present in the region of the left kidney.

At this time, and on examination of the preliminary film, a diagnosis of aneurysm of the left renal artery was made.

The remainder of the history was without relevant findings except that she had undergone a hysterectomy for fibroids in 1949.

The physical examination was essentially negative except for the tenderness elicited on palpation in the left hypochondrium. The tenderness was only in the anterior aspect of the abdomen on the left side and the flank was negative to palpation. Since she was not obese, it was not too difficult to outline a mass in the region of the left kidney. There was no bruit audible. The right kidney was not palpable and there were no other pathologic findings.

The blood pressure was 132/72 and there were no cardiac irregularities. The urine, blood count, blood serology and blood chemistry all were normal. An ecchinococcus complement fixation test was also negative. The sedimentation rate was 5 millimeters.

An excretory urogram (fig. 1, *A*) disclosed the ring-like shadow on the preliminary film to be closely associated with the upper mesial aspect of the left kidney. The 15 minute film (fig. 1, *B*) showed a smooth compression defect of the upper mesial aspect of the left renal pelvis, indicating that this separate mass probably occupied the sinus renalis, so producing the defect in the renal pelvis. The right kidney, ureters and bladder appeared normal. Retrograde pyelography on the left side gave no added information except to confirm the above described lesion. Kidney function was normal and urine cultures were sterile.

On May 28, 1954, the patient was admitted to the New York Polyclinic Hospital where an attempt was successfully made to prove that the ring-shadow

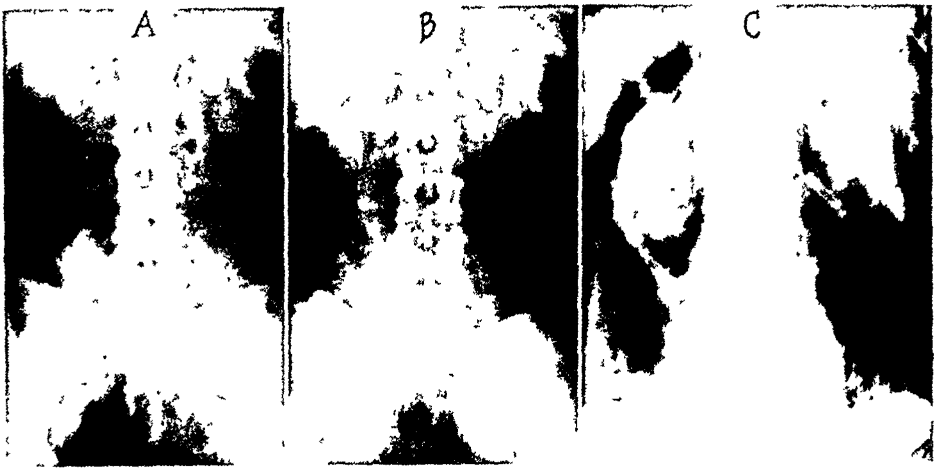

Fig. 1. *A*, preliminary film. Appearance of ring-like shadow. *B*, 15 minute film. Compression defect of left renal pelvis. *C*, perirenal oxygen injection showing radiolucent center of aneurysmal ring.

was a part of the vascular system of the kidney. If, on aortography, the radiolucent center could be made radiopaque, then the diagnosis of renal artery aneurysm was certain.

Accordingly, the patient was properly prepared and on May 28, under local anesthesia, about 750 cc of oxygen were injected according to the technique of Rivas. Within one hour, flat x-rays taken showed excellent dissemination of the oxygen around both kidneys (fig. 1, *C*). The ring-shadow now was more pronounced. At this time the patient was anesthetized using pentothal sodium, and in the routine used by Dr. J. S. Ritter, a needle was inserted into the aorta above the coeliac axis and aortograms were made using 80 per cent sodium iodide.

Figure 2 shows adequate visualization of the aorta, the coeliac axis and its branches. The right renal artery is normally visualized as is the vascular architecture of this organ. On the left side, the renal artery is small and barely discernible and leads directly into this opaque ring-shadow. The radiolucent center of the ring is now radiopaque, filled with the iodide injected into the aorta. Proof, then, that the ring-shadow is of the vascular supply of the kidney, the center of which contains blood. The remainder of the renal arcades are diminutive and scarcely seen. The kidney itself appears smaller than its fellow on the right. There were no other changes in the remainder of the vessels visualized.

The patient was re-admitted to the hospital and on June 9 was subjected to a nephrectomy.

The patient was placed in the usual kidney position as for nephrectomy and an incision in the skin was so placed and extended for a distance considered sufficient either for elongation or easy removal of ribs. Neither was necessary. The kidney was delivered in the usual manner, except that the peritoneum on the anterior aspect of this organ was widely freed and easily packed away. Figure 3, taken at the time of operation, demonstrates the position of the an-

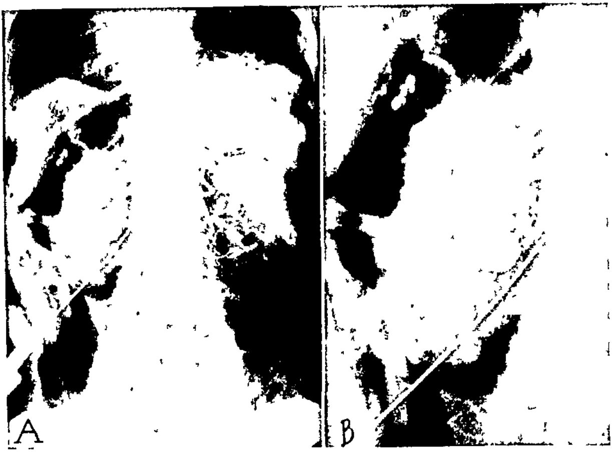

Fig. 2. *A*, aortogram following perirenal oxygen injection; "opacification of ring." Visualization of normal right renal architecture. *B*, magnified view of left kidney showing opacification or ring and diminutive renal architecture.

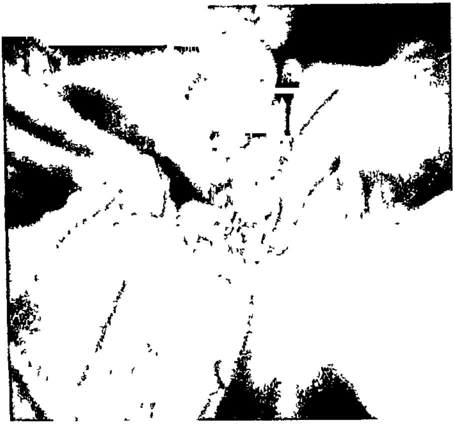

Fig. 3 Aneurysm in situ. Bulge of aneurysm indicated by nose of Kelly clamp.

eurysm in situ. Contrary to customary location, it appeared on the posterior surface of the kidney and was about the size of a plum. It almost completely occupied the sinus renalis and so displaced the renal pelvis laterally and the vein upward. The renal artery was palpated above and on the medial aspect as it came off the sac eccentrically. This vessel was easily followed up to the aorta and appeared to be small and firm to the touch. The two small distal vessels

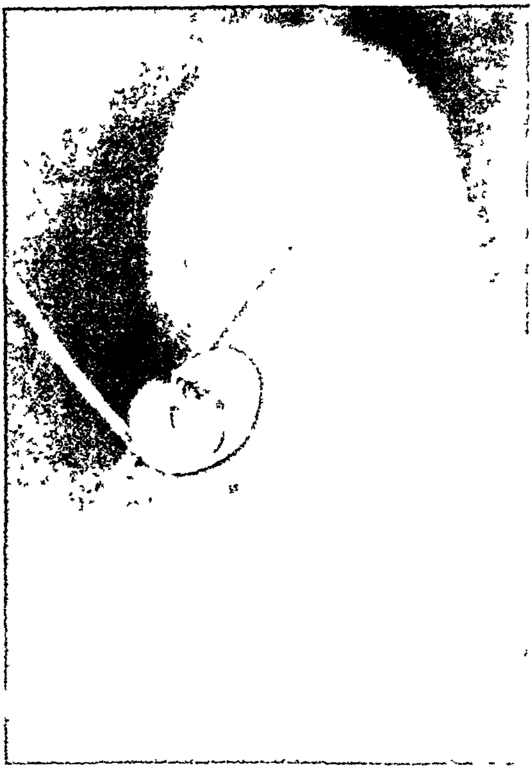

FIG. 4 X-ray of surgical specimen exhibiting uncapped aneurysmal sac and showing tiny efferent vessels containing No. 6 ureter catheters.

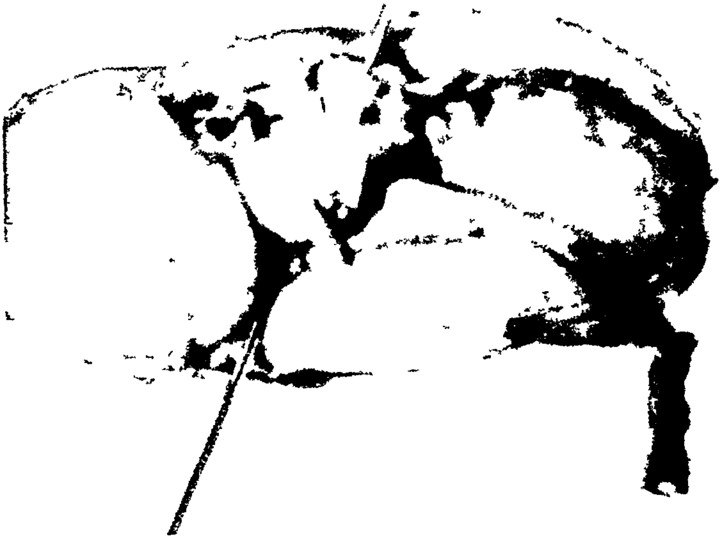

FIG. 5. Photograph of surgical specimen. Dark lines indicate tiny vessels leaving and entering uncapped aneurysm Compressed renal pelvis under lower border of aneurysm.

that emerged from the sac were tiny and buried in the parenchyma. It was deemed advisable at this point to do a nephrectomy which was carried out in the routine manner.

The postoperative course was uneventful and the patient left the hospital in 9 days.

X-rays taken of surgical specimen (fig. 4) exhibit the uncapped aneurysmal sac showing tiny efferent vessels, the sole blood supply to the kidney, containing No. 6 ureter catheters. A photograph of the surgical specimen is depicted in figure 5.

Pathological report: "The renal vein and its tributaries are grossly normal. The renal artery, just prior to the hilum and its bifurcation into its two main branches, forms a saccular aneurysm measuring 2.5 cm. in diameter. On palpation, it is firm, yellowish-white, cartilaginous in consistency. On cut section, its inner surface is smooth to roughened, yellowish-white. The wall is thickened, yellowish-white, in places calcified, measuring up to .8 cm. in thickness.

"Microscopic examination: Multiple sections from the renal aneurysm show a thickened intima with areas of hyalinized, fibrous connective tissue alternating with dense acellular fibrous connective tissue, for the most part calcified with areas of bone formation. Sections taken from normal artery and aneurysm show frayed, fragmented internal elastic membrane with intimal sclerosis and degenerating musculature. The interlobular and arcuate arteries show varying degrees of intimal sclerosis."

SUMMARY

A case of true aneurysm of the renal artery has been presented. Particular attention is directed to the possibility of more accurate diagnosis when perirenal oxygen insufflation and aortography are employed. "Opacification of the ring", on aortography of circular shadows in or near the kidney should be considered as evidence of renal artery aneurysm.

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A NEW CONCEPT IN URETHRAL SOUND CONSTRUCTION

GEORGE W. IRMISCH

The Le Fort follow-up sound is one of the indispensable urologic instruments for diagnostic and therapeutic work. The filiform guide has prevented many injuries particularly when sounds are passed through the unexplored urethra. In private practice, the advantages of this instrument are well known.

Urologists are familiar with the cumbersome, awkward cranking motion necessary to engage and disengage the sound from the filiform tip. Since this sound is most useful when dilating strictures of small caliber, multiple sounds of increasing diameter must be engaged. When one is working in a busy clinic, where many urethral dilatations and calibrations are being performed, this cranking movement is time-consuming and laborious. The screw tip frequently becomes worn and difficult to engage since the entire sound must be rotated. This is even more difficult because of the lubrication. It is during such periods that one contemplates new methods and instruments. Wilford A. H. Councill, Jr. recently suggested a new type of coupling for the filiform tip.

This paper is to present an entirely new concept in sound construction. The Le Fort sound is solid and has a male screw tip. The Irmisch sound, which I am describing, is hollow and the screw tip is actually the small end of a cable which terminates in a larger end which is a knurled thumb screw in the handle of the sound (fig. 1, *A*).

The filiform of standard design is passed through the urethra as usual and held with the fingers of the left hand. The tip of the new Irmisch sound is held in apposition to the filiform in order to engage the screw end. Now, instead of all the cranking motion, the operator merely turns the thumb screw contained in the handle with the thumb and index finger of the right hand. This rotates the cable within the sound and the filiform is easily and rapidly engaged. It is disengaged by a similar maneuver.

The sound is manipulated swiftly and easily and all awkwardness is avoided. This sound should outlive the Le Fort sound which, being constructed in one piece, must be discarded when the screw tip wears. Some instrument companies will replace the worn threads on a Le Fort sound but the repair is never so satisfactory as a new one and they have been known to break off.

With this new instrument, a worn thread is easily corrected by replacing the cable but the sound itself remains in use.

Cleaning and sterilizing are facilitated since the cable may be withdrawn from the instrument. When sounds are kept in a constant sterilizing bath, the cable may be withdrawn just enough to allow the solution to flow to all surfaces (fig. 1, *B*).

SUMMARY

A new concept in the manufacture of urethral sounds is presented. The effectiveness and advantages of the Le Fort type of follow-up sound are acknowledged.

Accepted for publication October 1, 1954.

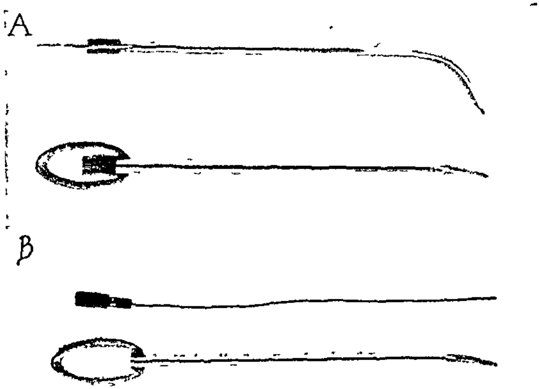

Fig. 1

This sound, which has been designated as the Irmisch sound by the manufacturer, utilizes the principle of the filiform guide and any filiform now made can be used with it. It relieves the urologist of all previous time-consuming and cumbersome maneuvers.

It is hoped that the introduction of this instrument will advance and encourage the use of the filiform technique in urethral calibration.

The writer wishes to express his thanks to C. R. Bard, Inc. for constructing this sound.

740 W. State St., Trenton, N. J.

REFERENCE

Councill, W A. H., Jr.: J. Urol., 70: 127, 1953.

THE JOURNAL OF UROLOGY
Vol 73, No 4 April 1955
Printed in U.S.A.

A NEW CONCEPT IN URETHRAL SOUND CONSTRUCTION

GEORGE W. IRMISCH

The Le Fort follow-up sound is one of the indispensable urologic instruments for diagnostic and therapeutic work. The filiform guide has prevented many injuries particularly when sounds are passed through the unexplored urethra. In private practice, the advantages of this instrument are well known.

Urologists are familiar with the cumbersome, awkward cranking motion necessary to engage and disengage the sound from the filiform tip. Since this sound is most useful when dilating strictures of small caliber, multiple sounds of increasing diameter must be engaged. When one is working in a busy clinic, where many urethral dilatations and calibrations are being performed, this cranking movement is time-consuming and laborious. The screw tip frequently becomes worn and difficult to engage since the entire sound must be rotated. This is even more difficult because of the lubrication. It is during such periods that one contemplates new methods and instruments. Wilford A. H. Councill, Jr. recently suggested a new type of coupling for the filiform tip.

This paper is to present an entirely new concept in sound construction. The Le Fort sound is solid and has a male screw tip. The Irmisch sound, which I am describing, is hollow and the screw tip is actually the small end of a cable which terminates in a larger end which is a knurled thumb screw in the handle of the sound (fig. 1, *A*).

The filiform of standard design is passed through the urethra as usual and held with the fingers of the left hand. The tip of the new Irmisch sound is held in apposition to the filiform in order to engage the screw end. Now, instead of all the cranking motion, the operator merely turns the thumb screw contained in the handle with the thumb and index finger of the right hand. This rotates the cable within the sound and the filiform is easily and rapidly engaged. It is disengaged by a similar maneuver.

The sound is manipulated swiftly and easily and all awkwardness is avoided. This sound should outlive the Le Fort sound which, being constructed in one piece, must be discarded when the screw tip wears. Some instrument companies will replace the worn threads on a Le Fort sound but the repair is never so satisfactory as a new one and they have been known to break off.

With this new instrument, a worn thread is easily corrected by replacing the cable but the sound itself remains in use.

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SUMMARY

A new concept in the manufacture of urethral sounds is presented. The effectiveness and advantages of the Le Fort type of follow-up sound are acknowledged.

Accepted for publication October 1, 1954.

Structure and Properties of Proteins Linus Pauling Ph D (by invitation), Professor of Chemistry, California Institute of Technology and Director of Gates and Crellin Laboratory of Chemistry, Pasadena Calif

Treatment of Acute Anuria T B Reynolds (by invitation), Assistant Professor of Medicine, University of California, Los Angeles, Calif

Motion Pictures 2 00 p m to 5 00 p m

Surgical Technique of Palliative Treatment of Prostatic Carcinoma with Radioactive Colloidal Chromic Phosphate Carl Rusche and (by invitation) Henry L Jaffe, Hollywood, Calif

Peristalsis by Cineradiography Frank Hinman, Jr and (by invitation) Earl R Miller and Lee B Lusted, San Francisco, Calif

Observations of Ureteral Obstruction and Contractility in Man and Dog John A Benjamin, Rochester, N Y

Excretory Urography as Visualized by the Image Intensifier Henry Bodner, Allan H Howard and (by invitation) Joseph H Kaplan, Los Angeles Calif

Ectopic Ureter Opening into a Seminal Vesicle Albert E Goldstein, Baltimore, Md

The Surgical Management of the Dilated Ureter in Children Charles M Stewart, Los Angeles, Calif

Simplified Technique for One Stage Suprapubic Prostatectomy Justin J Cordonnier, St Louis, Mo

The Foley Y Plasty and Mechanism of Anomalous Vessel Obstruction Frederic E B Foley, St Paul, Minn

Dependent Perineal Drainage in Retropubic Prostatectomy Richard Chute, Boston, Mass

WEDNESDAY, MAY 18

Motion Pictures 8 00 a m to 9 00 a m

Trans Rectal Biopsy of the Prostate Harry Grabstald (by invitation), Cleveland, Ohio

Genital Ablation for Carcinoma of the Male Urethra Donald C Malcolm (by invitation), Long Beach, Calif

Extraperitoneal Nephro Ureterectomy by Anterior Abdominal Incision Henry Bodner, Allan H Howard and (by invitation) Joseph H Kaplan Los Angeles, Calif

Perineal Abdominal Radical Cystectomy Wyland F Leadbetter and (by invitation) Burdick G Clarke, Boston, Mass

Scientific Sessions 9 00 a m to 12 30 p m

Amyloidosis of the Lower Genito Urinary Tract A Clinical and Pathological Study Norris J Heckel and (by invitation) James H McDonald, Chicago, Ill

Discussion Richard Chute, Brookline Mass

Studies of the Urinary Sphincters and the Control of Urination Francis A Beneventi and Victor F Marshall, New York, N Y

Discussion Joseph Fischmann Boston, Mass

Exstrophy of the Urinary Bladder, Its Treatment by Plastic Surgery T H Sweetser and (by invitation) Tague C Chisholm Willis H Thompson, Eldon B Berglund Stanley P Wesolowski and T H Sweetser Jr Minneapolis Minn

Discussions Charles C Higgins, Cleveland, O , Tracy O Powell, Los Angeles Calif

URINARY TRACT INFECTIONS: METHOD FOR RAPID SELECTION OF MOST EFFECTIVE DRUGS. William C. Casey, John P. Burnham and Donald Burke (by invitation) Torrance, Calif.

DIAGNOSTIC STEPS IN DIFFERENTIATION OF KIDNEY TUMORS. Truman E. Caylor, Wallace Tirman, Robert Bishop and Charles H. Caylor (by invitation), Bluffton, Ind.

SURGICAL MANAGEMENT OF THE DILATED URETER IN CHILDREN. Donald A. Charnock, Herman I. Riddell, Charles M. Stewart and (by invitation) Glen H. Gummess, Los Angeles, Calif.

DEPENDENT DRAINAGE VIA THE PERINEUM FOLLOWING RETROPUBIC PROSTATECTOMY. Richard Chute, Boston, Mass.

WIRT B. DAKIN HISTORICAL MUSEUM OF THE AMERICAN UROLOGICAL ASSOCIATION. Wirt B. Dakin, Los Angeles, Calif.

A FOLLOW-UP STUDY OF HORSESHOE KIDNEY SURGERY. Franklin Farman and (by invitation) Leslie Kamens, Whittier, Calif.

HISTORICAL UROLOGICAL INSTRUMENTS. Edward E. Ferguson and F. K. Mostofi, Washington, D. C.

A REPORT OF ELECTRON MICROSCOPE STUDIES OF HUMAN URINE. George M. Fister and (by invitation) George W. Cochran, Ogden, Utah

RENAL AND URETERAL SURGERY WITHOUT INTUBATION: CLINICAL AND EXPERIMENTAL STUDY. Frank C. Hamm and (by invitation) Sidney R. Weinberg, Brooklyn, N. Y.

THE SMOOTH MUSCLE IN URETERAL REGENERATION. Frank Hinman, Jr. and (by invitation) Rudolf Oppenheimer, San Francisco, Calif.

PHYSIOPATHOLOGY OF THE RECTAL BLADDER. Frank Hinman, Jr. and (by invitation) Gilbert I. Smith, San Francisco, Calif.

A NEW CONCEPT IN URETHRAL SOUND CONSTRUCTION. George W. Irmisch (by invitation), Trenton, N. J.

ABDOMINAL VENOGRAPHY IN UROLOGY. Joseph J. Kaufman, John Watkins and Donald Burke (by invitation), Los Angeles, Calif.

CYSTOURETHROGRAPHY: IMPORTANCE OF THE VOIDING CYSTOURETHROGRAM. Joseph J. Kaufman, Murray Russell and Hyman Peck (by invitation), Beverly Hills, Calif.

NITROFURANTOIN: CLINICAL AND LABORATORY CONSIDERATIONS. Paul F. MacLeod and George S. Rogers (by invitation), Norwich, N. Y.

RENAL RESECTION FOR TUBERCULOSIS. Donald C. Malcolm (by invitation), Long Beach, Calif.

DIATRIZOATE SODIUM (HYPAQUE): AN IMPROVED MEDIUM FOR EXCRETORY UROGRAPHY. Thomas D. Moore and Raymond F. Mayer, Memphis, Tenn.

EXPERIENCE WITH THE JOHANSON URETHROPLASTY. John J. Murphy, Jose Figueroa-Colon, Morton Bogash and William Oldham (by invitation) and Paul R. Leberman, Philadelphia, Pa.

CALCULUS DISEASE OF THE URINARY TRACT. Norman Nelson (by invitation) and R. Theodore Bergman, Los Angeles, Calif.

TABLE-SUPPORTED RETRACTOR: TIDAL IRRIGATOR: IMPROVED SUCTION TIP METHOD OF KEEPING TRACK OF SPONGES DURING THE OPERATION: REVAMPED COMPRESSION BELT FOR EXCRETORY PYELOGRAPHY. The O. A. Nelson Group, Seattle, Wash.

A NEW CYSTOSCOPE HOLDER. John F. Perez (by invitation), Atlantic City, N. J.

Treatment of Carcinoma of the Bladder With Cobalt^{60} Beam Therapy. L. E. Plank, J. W. Grossman and J. L. Howarth (by invitation), Albuquerque, N. M.

Nesbit Technique of Transurethral Resection of Prostate. Robert T. Plumb, San Diego, Calif.

Ureteral Reconstruction With Split Skin Grafts: an Experimental Study. Victor A. Politano and Charles E. Horton (by invitation), Durham, N. C

Medical and Surgical Treatment of Cryptorchidism. Robert J. Prentiss and Ralph B. Mullenix and (by invitation) James M. Whisenand and Michael J. Fenney, San Diego, Calif.

Electrolyte Reabsorption From the Normal and Artificial Cloaca. Samuel I. Roland, James Niebel and Milton L. Rosenberg (by invitation), San Francisco, Calif.

Hyperparathyroidism, A Curable Disease, with Emphasis upon the Renal Manifestations of the Disease. Robert W. Schneider and L. J. McCormack (by invitation), Cleveland, O.

Effect of Oxysteroids (DOCA, Compounds E, F and S) on the Inhibitory Action of Antibiotics on Cultures of Bacteria and E. Histolytica. Harry Seneca and Ellen Bergendahl (by invitation), New York, N. Y.

Free-Flow Versus Sphincteric Mechanisms in Ureteral Transplantation. Donald R. Smith and (by invitation) Robert Whitrock and Alvin Rutner, San Francisco, Calif.

Osseous Phlebography in Conditions of Urologic Interest. Donald R. Smith and (by invitation) H L. Steinbach, N. L Petrakis, R. S. Gilfillan and P. A. Lahr, San Francisco, Calif.

Delayed Cystography. Charles M. Stewart, Los Angeles, Calif.

Technique of Transurethral Prostatic Resection. Roderick Turner (by invitation), Roger W. Barnes, R. T. Bergman and (by invitation) Henry L. Hadley, Los Angeles, Calif

Clinical Features and Chemical Morphology of Semen and Some of Its Variations. Edward T. Tyler and Heron Singher (by invitation), Los Angeles, Calif.

Fixation of the Urine Reaction as a Factor in the Cause and Management of Urinary Calculi Julius H Winer, Beverly Hills, Calif.

Organization of a Stone Registry, with Demonstrations of Analytical Methods. Hans H Zinsser and Harold Frankl (by invitation), and Donald A. Charnock and Jay J Crane, Los Angeles, Calif.

TECHNICAL EXHIBIT

Mr. William P. Didusch, *Chairman*

NAME AND ADDRESS OF FIRM	BOOTH NUMBER
American Cystoscope Makers, Inc., New York, N. Y.	25, 26, 27, 28, 29, 30, 31
Astra Phamaceutical Products, Inc , Worcester, Mass.	6
Ayerst Laboratories, New York, N. Y.	34
C. R. Bard, Inc., Summit, N. J.	18, 19, 20
The Birtcher Corporation, Los Angeles, Calif.	1, 2
Coca-Cola Company, Atlanta, Ga.	36
Hoffmann-LaRoche, Inc., Nutley, N. J.	12

Liebel-Flarsheim Company, Cincinnati, O. . . . 22, 23
Mallinckrodt Chemical Works, St. Louis, Mo. . . . 13, 14
V. Mueller and Company, Chicago, Ill. . . . 15, 16
National Electric Instrument Co. Inc., Elmhurst, N. Y. . . . 4, 5
Nepera Chemical Company, Inc., Yonkers, N. Y. . . . 21
Parke, Davis & Company, Detroit, Mich. . . . 24
Pfizer Laboratories, Brooklyn, N. Y. . . . 8
Radium Chemical Company, Inc., New York, N. Y. . . . 35
The Radium Emanation Corporation, New York, N. Y. . . . 32
W. B. Saunders Company, Philadelphia, Pa. . . . 11
Schering Corporation, Bloomfield, N. J. . . . 17
Sharp & Dohme, Division of Merck & Co., Philadelphia, Pa. . . . 3
E. R. Squibb and Sons, New York, N. Y. . . . 7
The Williams & Wilkins Co., Baltimore, Md. . . . 33
Winthrop-Stearns, Inc., New York, N. Y. . . . 9, 10

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HYPERTENSION DUE TO RENAL COMPRESSION RESULTING FROM SUBCAPSULAR HEMATOMA

WILLIAM J. ENGEL AND IRVINE H. PAGE

From the Department of Urology and the Research Division, The Cleveland Clinic Foundation and The Frank E. Bunts Educational Institute, Cleveland, Ohio

In 1939, Page[1] demonstrated that experimental hypertension could be produced in an animal by wrapping one of its kidneys in cellophane which resulted in the formation of thick, dense, scar tissue around the kidney. Page pointed out that the hypertension did not result from compression of the renal artery, but rather from changes in intrarenal hemodynamics produced by the firm hull surrounding the parenchyma. In a dog having hypertension that is produced in this manner, removal of the kidney usually results in the return of the arterial pressure to normal levels. Page suggested in that same report that the clinical counterpart of the hypertension he described might be found in organizing hematomas following perirenal hemorrhage resulting from accidental or perhaps severe surgical damage to the kidney. The case to be described appears to represent this type of problem.

A 19 year old man was first seen by Dr. John Tucker of the medical department on September 9, 1953. The patient's presenting complaint was headache. Two years before our examination, his college entrance physical examination had shown him to be hypertensive. Since that time, his blood pressure had ranged between 170/110 and 158/90 mm. Hg, at no time was it found to be normal. Four months before examination, he began to have occipital headache that occurred primarily in the late afternoon, was relieved by aspirin, and usually was associated with stiffness of the posterior muscles of the neck. The family history was negative for hypertensive vascular disease, with the exception that one paternal aunt had hypertension at the age of 58. The patient could remember no injuries; there was no history of flank pain, no hematuria, and no nocturia. He had played football during his high school years, and although there was no definite history of injury to the kidney, he stated that after a game he frequently had had pain and soreness in various locations.

Physical examination revealed a healthy appearing young man who was 68 inches in height and weighed 149½ pounds. His blood pressure was 168/110 mm. Hg. Examination of the ocular fundi revealed a grade II arteriolar constriction, no sclerosis, no hemorrhages and no exudates. The left border of cardiac dullness was 8.5 cm. from the midsternal line in the fifth intercostal space. There were no murmurs. The aortic second sound was louder than the pulmonic second sound. The lung fields were clear. The findings on examination of the abdomen were normal.

Read at annual meeting, North Central Section of American Urological Association, Detroit, Mich. October 7–9, 1954.

[1] Page, I. H. Method for producing persistent hypertension by cellophane. Science, 89: 273–274, 1939. Also Page, I. H. Production of persistent arterial hypertension by cellophane perinephritis. J. A. M. A., 113: 246–248, 1939.

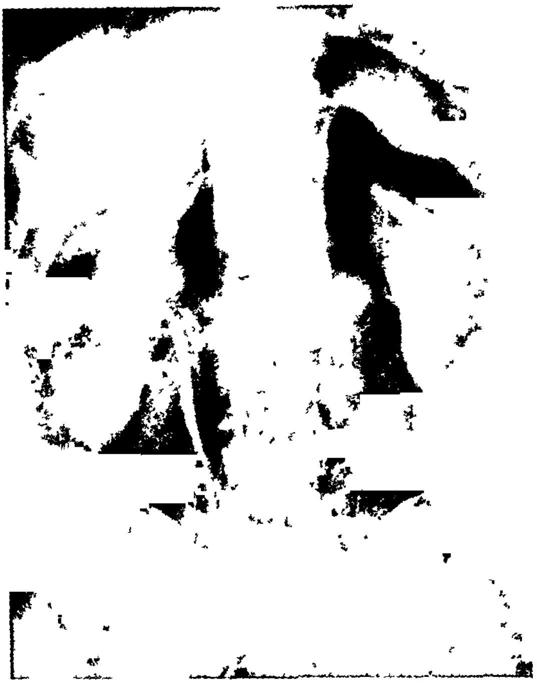

FIG. 1. Retrograde right pyelogram made following presacral oxygen insufflation. Note deformity of pelvis and also striated calcifications along lateral margin of kidney. Renal outline shows no tumor.

Roentgenographic examination of the chest showed the transverse cardiac diameter to be within normal limit; the lung fields were clear. An x-ray film showed both kidneys to be in normal position. The entire right kidney seemed to be covered with many linear streaks of calcification up to 5 mm. in width. An excretory urogram done with neo-iopax showed prompt excretion of the dye on both sides, and the total function appeared to be normal. The left renal pelvis was normal. The right renal pelvis was atypical, with flattening of some calyces which suggested compression. Presacral oxygen insufflation gave good contrast outline of the right kidney and indicated that the calcifications were limited to the renal outline (fig. 1).

The hemoglobin content was 16 gm. per cent with a cell volume of 51 cc; the white blood cell count was 5,300. An Addis count was made: the specific gravity was 1.035; there was 0.08 gm. of protein per 24 hours; no red cells; 550,000 white cells; and no casts per 12 hours. The blood urea was 21 mg. per cent. A mannitol-para-aminohippurate clearance was done: the renal blood flow was 1451 cc per minute, the plasma flow 825 cc per minute, the glomerular filtration rate 141 cc per minute with a filtration fraction of 0.17. A test of vascular responsiveness to many vasoactive agents was performed with the blood pressure being recorded from a catheter placed in the brachial artery. The administration of repeated doses of tetraethylammonium, starting with 1.25 mg. per kilogram and increasing to 2.5 mg. per kilogram, revealed no evidence of increased neurogenic tone. With the first dose of TEA, there was a slight depression in blood pressure, but the three consecutive doses of 2.5 mg. per kilogram gave only pressor responses. This pattern is distinct from that seen in experimental animals with neurogenic hypertension and is similar to that seen in animals with experimental renal hypertension. In animals with experimental neurogenic hypertension, repeated intravenous doses of TEA cause repeated depressor responses, while in animals with experimental renal hypertension, the first injection of TEA may give a depressor response, and, following this, pressor responses are rapidly obtained. There was no appreciable response to intravenous serotonin either before or after TEA; this also followed the pattern of experimental renal hypertension.

A right nephrectomy was advised. The kidney was exposed through the usual lumbar incision with removal of the twelfth rib. The kidney was found to be completely surrounded by a hard, bonelike shell that extended all the way around to the hilus of the kidney, but there was no evidence of compression of the renal vessels. It was impossible to remove the shell without sacrificing the kidney, and therefore a nephrectomy was performed.

The pathologic examination of the kidney that was removed was reported as follows: Gross: "Submitted is the right kidney weighing 220 gm. and measuring 11.0 by 6.5 by 2.9 cm. The capsule is firmly adherent to the cortex. On palpation, the cortex in its periphery feels firm and calcified. Section reveals a large capsular cyst, measuring 9.9 cm. in greatest diameter. Its wall is firmly calcified. It is filled with a thick golden fluid. The remaining renal parenchyma has a peculiar dull brown appearance; the renal cortex measures 1.3 cm. in thickness; the cortex and medulla, 3.3 cm. in thickness" (fig. 2). Microscopic: "A section of

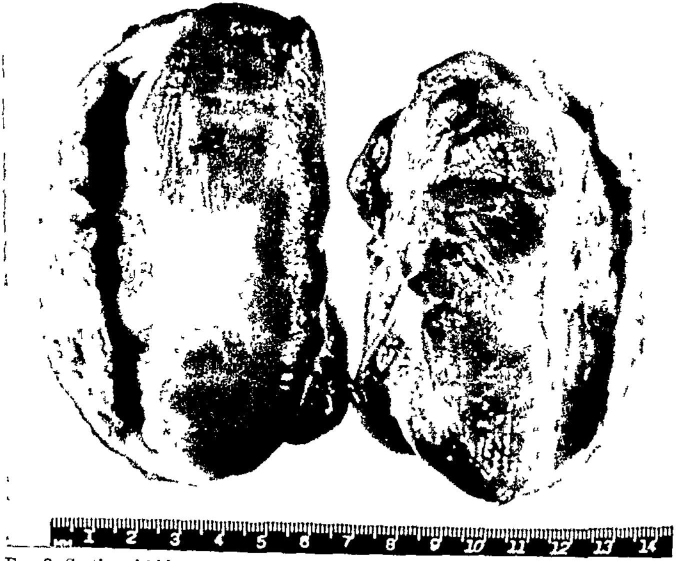

FIG. 2. Sectioned kidney removed at operation. Subcapsular cyst surrounded by dense zone of calcification is present. Note absence of any demarcation between renal cortex and medulla.

decalcified cyst wall reveals it to be made up of dense fibrous tissue in part vascularized. There are occasional lymphocytic foci, and in one area there is heterotopic bone formation containing normal cellular marrow. The adjacent fatty tissue contains fresh hemorrhage."

Sections of the kidney showed subcapsular fibrosis and focal lymphocyte deposits. There was an occasional scarred glomerulus. Here and there an arteriole was thickened and hyalinized. The final pathologic diagnosis was calcified old perinephric hematoma, heterotopic bone formation, chronic nephritis, necrotizing arteriolitis.

During the first 5 days of the patient's hospital stay preceding operation, the blood pressure averaged 140/89 mm. Hg, and ranged between 156 and 120 systolic and between 102 and 80 diastolic. During the first week following nephrectomy, his blood pressure averaged 118/72 mm. Hg, the systolic range was 130 to 100 and the diastolic 90 to 64 mm. Hg. The postoperative course was completely uneventful.

Follow-up examinations during the year since operation have revealed normal blood pressure levels (range of 100 to 130 systolic, and 64 to 90 diastolic). Renal excretory functional tests 4 months after operation were normal.

DISCUSSION

It would seem that this case clearly is a clinical example of the "cellophane kidney" of experimental hypertension. Relatively few examples have appeared in the literature. Farrell and Young[2] reported hypertension in a boy following injury to the right kidney. At operation a large cyst surrounded the kidney. The cyst wall that was made up of firm, collagenous tissue tightly held the renal parenchyma. Removal of the kidney reduced the arterial pressure to normal.

A case is described by MacKay, Proctor and Roome[3] in which a fibrous hull developed around a kidney following operation for removal of a renal calculus. The unusual density was attributed to a B. proteus infection. Severe hypertension developed which was cured by nephrectomy. Hayward[4] reported a case of hypertension that developed following a plastic operation for hydronephrosis, and he warned of the possible danger of the development of hypertension following renal surgery. In view of the large number of renal operations being performed, this type of hypertension must be regarded as a rare complication. The possibility of its development, however, should remind us of the importance of avoiding undue surgical trauma to the kidney and its capsule, and the advisability of performing operations without completely delivering the kidney into the incision, whenever possible.

It is well to point out that not all perirenal hematomas produce hypertension and we have seen many which did not. Transient hypertension has been noted with perirenal hematoma which returns to normal with reabsorption.[5, 6] It is reasonable to assume that subcapsular hemorrhage is more likely to produce renal compression than is extracapsular hemorrhage that has the free retroperitoneal space in which to expand. We have seen several extracapsular hematomas, both recent and old, showing no tendency to produce hypertension.

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[2] Farrell, J. I. and Young, R. H.: Hypertension caused by unilateral renal compression. J.A.M.A., **118**: 711–712, 1942.

[3] MacKay, A., Proctor, L. D. and Roome, N. W.: Hypertension after removal of a renal calculus. Can. M. A. J., **50**: 328–331, 1944.

[4] Hayward, W. G.: Renal surgery as cause for renal ischemia. J. Urol., **51**: 486–490, 1944.

SUMMARY

A case of hypertension in a 19 year old man is presented which was cured by removal of a kidney that was being compressed by an old, calcified, subcapsular hematoma.

This example, together with other reported clinical cases, leaves little doubt that unilateral renal compression can produce hypertension that may be severe. It appears to be comparable to experimental hypertension produced by wrapping a kidney in cellophane or similar material which produces a thick fibrous hull around the kidney.

It is suggested that subcapsular hemorrhage and hematoma are more likely to produce hypertension than is perirenal hematoma. It is also pointed out that not every perirenal hematoma produces hypertension.

There is no reason to believe that calcification demonstrable on roentgenograms is an essential diagnostic feature. A thick, fibrous, radiolucent envelope surrounding the kidney could produce hypertension.

Our patient, although a high-school football player, gave no history of specific renal injury and never had had gross hematuria. This suggests the importance of careful inquiry as to possible renal trauma in patients with recent hypertension, especially in the young age groups.

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[5] Killian, S. T. and Calvin, J. K.: Renal hypertension in children; clinicopathologic studies. Am. J. Dis. Child, **62**: 1242–1272, 1941.

[6] Sobel, I. P.: So-called essential hypertension in childhood. Am. J. Dis. Child, **61**: 280–299, 1941.

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MECHANISMS OF HYDRONEPHROSIS: NEWER INVESTIGATIVE TECHNIQUES

LESTER PERSKY, JOHN P. STORAASLI AND GEORGE AUSTEN JR.

From the Department of Surgery, Division of Urology, and the Department of Radiology, University Hospitals and Western Reserve University School of Medicine, Cleveland, Ohio

As defined by Hinman, "hydronephrosis is the term applied to the renal changes of distension and atrophy which follow urinary obstruction. The fluid causing the distension is urine, and the condition presupposes continued secretion of urine in spite of the obstruction." Complete obstruction of the excretory duct of other glands of the body is followed by a primary type of atrophy without appreciable dilatation and with almost immediate cessation of function of the organ involved. This type of atrophy does not occur when the kidney is similarly treated. Investigation has revealed that the development of hydronephrosis and hydronephrotic atrophy is possible because of the reabsorption of contents from the renal pelvis. This phenomenon prevents intrapelvic pressure from rising above the level of effective filtration pressure and thereby allows continued production of urine.

In spite of the vast body of clinical and experimental data which has been accumulated on the subject of hydronephrosis, certain mechanisms permitting continued function of the obstructed kidney remain obscure. In a recent review of the subject,[1] Prather has summarized the basic contributions to this study of Hinman, Fuchs, Narath and others,[2, 3, 4, 5, 6] and he has outlined the defects in our present concept of the mechanics of this process. Although reabsorption or backflow may apparently occur by one or more of several mechanisms, this review emphasizes the fact that evidence is lacking to demonstrate whether one of these plays a more important role than another and/or whether any one of them has a selective function at any particular stage in the course of the process. It is apparent that the content of the obstructed renal pelvis is not simply an accumulation of normal urine, for it becomes more dilute as the degree of hydronephrosis progresses, and eventually it is essentially nothing but water and salt. Also, it has been shown that certain parts of the content of the hydronephrotic sac ultimately gain entrance into the circulating blood stream.

In an attempt to clarify this problem, we have experimentally utilized radioactive tracer techniques which, it was anticipated, would permit a definitive tracing of the transportation of pelvic contents that are apparently returned to

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Read at annual meeting, North Central Section of American Urological Association, Detroit, Mich., October 7-9, 1954.

[1] Prather, G. C.: Medical progress. Hydronephrosis. New Eng. J. Med., **250:** 944-952, 1954.

[2] Hinman, F.: Hydronephrosis. I. The structural changes. Surgery. **17:** 816-835, 1945.

[3] Hinman, F.: Hydronephrosis. II. The functional changes. Surgery, **17:** 836-845, 1945.

[4] Fuchs, F.: Pyelovenöser Reflux und Hydronephrose. Eine Untersuchung über die Pathogense der Sacknieren. Deutsche Ztschr. f. Chir., **224:** 353-382, 1930.

[5] Narath, P. A.: The hydromechanics of the calyx renalis. J. Urol., **43:** 145-176, 1940.

[6] Tuffier, M.: Étude Clinique et Experimentale sur L'hydronephrose. Ann. des Mal. Org. Génito-Ur. **12:** 14-40, 1894.

the blood stream. In addition, we hoped to determine more accurately the onset, rate and amount of reflux in relation to the degree of intrapelvic pressure and to correlate the influence of molecular or particle size with this phenomenon. A preliminary report of initial observations derived from this study is presented herewith.

MATERIAL AND METHOD

All of the experiments were carried out on healthy mongrel dogs weighing from 10 to 12 kilograms. Under nembutal anesthesia, acute and complete obstruction was created by ligating the ureter close to the ureteropelvic junction around a tube leading to a mercury manometer. As a component part of the apparatus, a special two-channel needle was designed which permitted the exchange of pelvic contents without change in intrapelvic pressure, as noted on the attached manometer. Observations were made over a period of one hour in each experiment. The animals individually received 200–300 cc of 5 per cent glucose in isotonic saline during the one hour period of study. When technical failures occurred or when easy exchange through the two way needle was not possible, the animal was discarded.

The dogs were divided into control and experimental groups. Two control animals were used to obtain simple pressure curves in the renal pelvis when the latter's contents did not contain radioactive material. The experimental animals were divided into four groups. Each of the first three groups was studied with one of three different radioactive materials. In the fourth group the three radioactive materials were employed in the absence of ureteral obstruction.

Three radioactive materials were used in this exercise in an attempt to obtain information regarding the influence of particle size on pelvic backflow. Normally, particles the size of sodium, molecular weight 23, and glucose, molecular weight 180, get back into the circulation. I^{131} as a sodium iodide, molecular weight 131, was used as a freely diffusible ion. Serum human albumen labeled with I^{131}, molecular weight roughly 50,000, a particle of larger size, was used to determine whether or not protein material could gain access to the blood stream. To determine whether or not colloidal particles could gain access to the circulating blood, radioactive colloidal gold (Au^{198}) was also used. The average size of the colloidal gold particles is $\frac{1}{10}$th micron, thus approaching macroscopic dimensions.

In the experimental group of animals, approximately 250 microcuries of radioactive material were used to irrigate the pelvis. In each case the radioactive material was diluted to approximately 30 cc for irrigation purposes. At the start of each experiment the pelvic content was replaced with the radioactive material to be studied. The manometer tubing was also filled with the isotopic substance to insure against dilution. In an attempt to have a constant concentration of radioactivity immediately adjacent to the pelviocalyceal mucosa, intermittent irrigations were carried out without modification of the pressures as read on the manometer. The two-way needle permitted aspiration and simultaneous injection of the radioactive material without change in pressure.

At the start of each experiment blood samples were obtained from the jugular

FIG. I

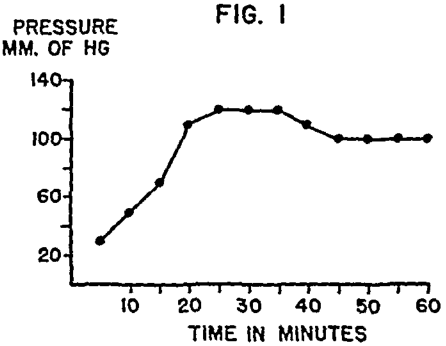

FIG. 2

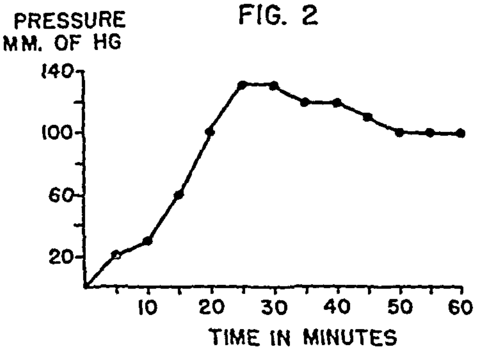

FIG. 1. Intrapelvic pressure curve, measured in mm. Hb. obtained during course of 60 minutes after complete obstruction of ureter in control dog.
FIG. 2. Same as figure 1.

vein of the animal, and repeat blood samples were taken every 5 minutes thereafter for 1 hour. Observed intrapelvic pressures were recorded at the time each sample of blood was obtained. Measurements of radioactivity of 3 cc samples of whole blood were made with a well-type scintillation counter, utilizing a thallium activated sodium iodide crystal.* The counts per minute of each sample were graphically correlated with the intrapelvic pressures read at the time the samples were withdrawn, as is noted in the accompaning graphs (figs. 1, 2, 3).

RESULTS

From the control animals, typical intrapelvic pressure curves were obtained following the experimental production of complete ureteral obstruction (figs. 1 and 2). The pressure rises fairly rapidly and usually falls after a peak has been reached at 15 to 20 minutes. The decline in pressure during the experimental period of 1 hour never reaches the initial low level. The pressure curves obtained in the experimental groups show the typical rise and fall in pressure as observed in the control animals.

Figures 3 through 6 illustrate the results obtained with iodinated albumen as the irrigating solution in the pelvis. The measurement of increasing radioactivity in the peripheral blood is a direct indication of pelvic reabsorption. The curves of radioactivity are superimposed on pressure curves obtained simultaneously to show the relationship of rise in blood concentration with the rise and fall in pelvic pressure.

Figures 7 and 8 show the results obtained when I^{131} as iodide was used under similar circumstances. Figures 9 and 10 give the results using radioactive colloidal gold. It should be noted that although there is definite evidence of radioactivity within the peripheral blood when using the latter material the concentration in no way approximates that obtained with the previously used isotopic materials. The explanation of this observation lies probably in the fact that colloidal gold is rapidly removed from the circulation by the reticuloendothelial system, especially that of the liver and spleen. To substantiate this conclusion, the liver, spleen, and kidney were assayed for radioactivity. The results are recorded in table 1.

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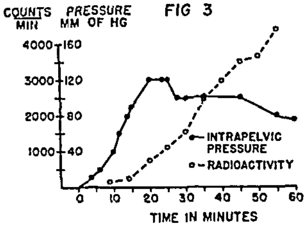
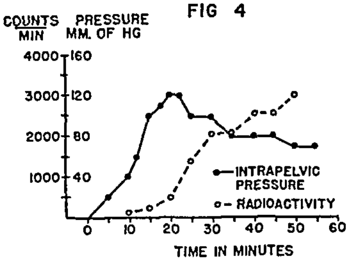
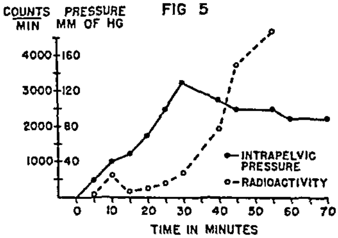
* The efficiency of the counting system was such that 1 microcurie of radioactive iodine gave approximately 900,000 counts per minute.







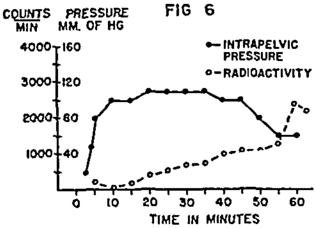
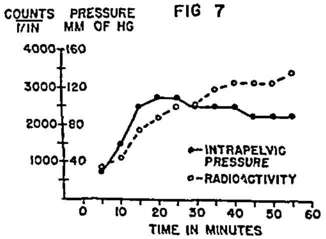


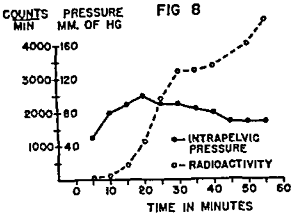
Fig 3 Curves depicting time correlation of changes in intrapelvic pressure and measurements of radioactivity of iodinated albumen in peripheral blood after complete obstruction of ureter and placement of test material in renal pelvis of dog

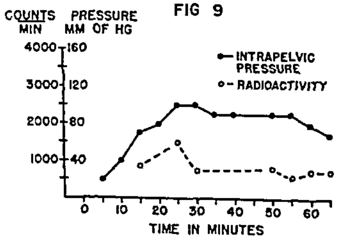
Fig 4 ●, Intrapelvic pressure ○, Radioactivity counts in peripheral blood

Fig 5 Same as figure 3

Fig 6 Same as figure 3







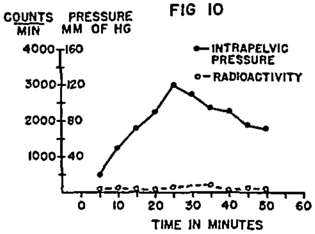


Fig 7 Curves depicting time correlation of changes in intrapelvic pressure and measurements of radioactivity of I^{131} in peripheral blood under same conditions as described in figure 3

Fig 8 Same as figure 7

Fig 9 Curves depicting time correlation of changes in intrapelvic pressure and measurements of radioactivity of colloidal gold (Au^{198}) in peripheral blood under same conditions as described in figure 3

Fig 10 Same as figure 9

TABLE 1. *Radioactivity measured in counts per minute recovered from reticuloendothelial system after colloidal gold has been placed in obstructed renal pelvis of dog*

	Exp. V	Exp. VIII
Liver	414,000	1,435,500
Spleen	42,350	295,042
Kidney	35,255	1,870,933

To obviate the possibility that I^{131} was separated from albumen in the experiment in which iodinated serum human albumen was used, periodic samples were assayed for radioactive protein bound content within plasma. It was found that 98 per cent of the radioactivity measured in the blood was in the protein bound form.*

DISCUSSION

The results obtained in these experiments corroborate the observation of others that reabsorption of pelvic contents does occur. The backflow or reflux of pelvic content is the explanation offered for the continued renal secretion of urine until hydronephrotic atrophy ultimately ensues and a fluid-filled sac remains. In this connection, it is of interest to note in our experiments that as the pressure within the pelvis falls the concentration of radioactivity in the peripheral blood continues to rise. However, the greatest blood concentration of radioactivity is achieved only after the pressure within the pelvis has reached a peak and has started to fall. In those instances in which the pressures remained high for a longer period of time (fig. 6), it can be seen by the low counts in the peripheral blood that backflow is at a minimum. On inspection of the curves obtained with ionic I^{131} alone (figs. 7 and 8), it appears as though the rise in radioactivity within the blood is far more rapid with this material than with the others and that retrograde diffusion takes place immediately. This is to be anticipated since one is using a freely diffusible ion. As was mentioned previously, the levels of radioactivity obtained with colloidal gold never approach the peak obtained with the other two isotopes, since the reticuloendothelial system of the liver and spleen rapidly remove the colloidal substance from the blood. This is evidenced by the high concentration of radioactivity obtained when these organs were assayed.

Mere contact of the radioactive material with the mucosa of the pelviocalyceal structures does not in itself permit reabsorption, since in nonpressure experiments low or no radioactivity could be detected within the peripheral blood. This confirms very early experiments in which strychnine, when placed in the renal pelvis, had no toxic effects upon experimental animals until ureteral obstruction had been effected.[6]

The rapidity with which backflow or reabsorption occurs is of importance since it may have some bearing on clearance techniques when applied in the presence of obstructive disease states. Selkurt has previously noted diminution in clearances during experimental increases in ureteral pressure.[7] No attempt was made to explore such techniques in these experiments.

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* The protein bound determinations were performed by precipitating the plasma protein fractions with trichloracetic acid, washing the filtrates three times with isotonic saline, and then measuring the radioactivity of the precipitate and comparing this to the total count obtained within the plasma.

That backflow or reabsorption of pelvic contents is not a simple diffusion process is evidenced by the fact that one is able to recover within the peripheral vascular system molecules of the size of albumen and particles of the order of $\frac{1}{10}$th micron. The fact that the radioactive colloidal gold gains access to the vascular system and distant reticuloendothelial structures supports the conclusion that, at least under the conditions of this experiment, the best explanation for the backflow is on the basis of a mechanism which permits ready access of pelvic contents to the blood stream rather than on the basis only of a pyelo-lymphatic or pyelo-interstitial backflow. It is a well known fact that colloidal gold, if injected subcutaneously or interstitially in other sites, remains relatively fixed in these areas.[8]

A possible route of transport which has been discussed is that of pyelotubular backflow. Some authors believe that there is a circulation of albumen within the tubules, and our studies do not completely eliminate this possibility. Certainly, in the case of iodinated albumen this could be a mechanism for backflow.[9] Early studies by O'Conor have shown that, in the presence of obstruction, India ink can be found in the proximal tubules.[10] Thus, a tubular circulation of albumen might be in effect here. However, it is unlikely that the tubular epithelium could handle particles the size of colloidal gold.

Several attempts to obtain radioautographs failed to illustrate the anatomical distribution of radioactivity in the kidney. Nevertheless, in one instance there was evidence of radioactivity uniformly dispersed around the pelviocalyceal structures, with some activity extending peripherally to the renal cortex beneath the capsule. It is possible that tears in the renal parenchyma, an experimental observation noted by Rolnick and Singer, is the route for backflow, and that the activity seen in the one radioautograph is a reflection of this phenomenon.[11] Before any conclusions can be drawn from this technique, further studies with modifications will have to be undertaken.

Further aims of this study should include investigations of rates and definitive routes of reabsorption and of renal clearances under conditions of prolonged obstruction in order to determine what differences exist between the acute and chronic preparation. A further corollary study would be the investigation of the influences of modifications of perirenal pressure on backflow measurements. It is anticipated that refinements in techniques would permit continuous radioactive flow measurements by utilizing various counting rate devices. This would allow for continuous measurements of radioactivity over the entire period of observation and permit absolute correlation with pressure changes.

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[11] Rolnick, H. C. and Singer, P. L.: Effects of overdistension of the renal pelvis and ureter. A study on pyelovenous backflow. J. Urol., **57**: 834–838, 1947.

SUMMARY

In summary, we may conclude from these studies of acute ureteral obstruction in animals that reabsorption of pelvic contents is a phenomenon which takes place rapidly and that it permits large particles to enter the blood stream. The nature of the particle size studied suggests that pyelovenous backflow is the main route of transport, and that for at least the larger particles there must be actual tears in the lining of the pelvis and adjacent vascular spaces.

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SURGICAL TREATMENT OF HORSESHOE KIDNEY: COMPARISON OF RESULTS AFTER VARIOUS TYPES OF OPERATIONS

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Successful surgical treatment of horseshoe kidney is no longer a novelty. The voluminous literature that has accumulated during the past 20 years abounds with accounts of gratifying postoperative results. Most of these, however, have been isolated case reports or analyses of very small groups of patients.

It is generally agreed that pathologic processes in either half of a horseshoe kidney deserve and demand the same therapeutic considerations as similar lesions in nonfused kidneys. There are widely divergent opinions, however, regarding the significance of the fusion per se and the value of some of the operations that have been proposed.

Although horseshoe kidneys are relatively common, most of these anomalies do not require surgical treatment. During the 15 years from 1939 through 1953, approximately one fourth of the horseshoe kidneys that were diagnosed at the Mayo Clinic were subjected to some type of operation.

It is not surprising, therefore, that the personal experience of most urologists in the surgical treatment of this anomaly has been rather limited and that the literature is devoid of critical comparison of different surgical techniques.

We have reviewed all of the cases of horseshoe kidneys that have been operated on at the Mayo Clinic. Other types of renal fusion, such as unilateral fused kidney and sigmoid or S-shaped kidneys have been excluded. In the early part of the twentieth century many horseshoe kidneys were noted as an incidental finding during abdominal operations or they were merely explored because of a palpable mass. Two such cases in which secondary nephrectomy eventually was performed have been included in our series but all other simple explorations have been excluded.

From 1912 through 1953, 106 patients with true horseshoe kidney had renal operations at this institution. It is this group which we have studied. Males predominated in a ratio of 4:1 (table 1). The youngest patient was 5 years of age and the oldest 65, but a little more than half of the total number were in the third and fourth decades.

All of the patients complained of pain, either in the flank or in the lower part of the abdomen. The indications for the initial operations performed at the clinic were: calculi (with or without hydronephrosis), 65 patients, hydronephrosis (without calculi) 27, tuberculosis 5, pain only 5, postoperative urinary fistula 2, and renal cyst 2. Eighty-seven per cent of the 106 patients had calculi or hydronephrosis or both.

Only 2 patients were suspected of having a renal neoplasm and in both cases the growth proved to be a simple cyst. One patient who died 17 years after

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Read at annual meeting North Central Section of American Urological Association, Detroit, Mich. October 7 to 9, 1954.

TABLE 1. *Age and sex distribution of 106 patients with horseshoe kidney operated on at the Mayo Clinic from 1912 through 1953*

Age, Years	Males	Females	Total
5	1	0	1
10–19	6	2	8
20–29	18	7	25
30–39	23	6	29
40–49	18	3	21
50–59	12	2	14
60–65	7	1	8
Total	85	21	106

pyelolithotomy was found to have an unsuspected carcinoma of the renal pelvis. One of the kidneys removed because of hydronephrosis contained an unsuspected hemangioma. These were the only renal neoplasms encountered in the entire group.

In 1 case the fusion involved the upper poles of the kidneys. In another instance the kidneys were said to be joined at the pelves. In all other cases some type of isthmus joined the lower poles.

The 106 patients included in this study had a total of 160 renal operations. Seventeen of these were performed elsewhere before the patients were seen at the clinic and 6 are known to have been performed elsewhere after the patients had been dismissed. The remaining 137 operations were performed at the clinic. Eighty-one of the 106 patients had only one operation at the clinic. Eleven individuals had single but separate procedures on both sides while 14 required more than one operation on one or both kidneys. Nearly 40 per cent of all patients, therefore, eventually had to have multiple operations.

Of the 137 operations at the clinic, the lumbar extraperitoneal approach was used in 128. Anterior extraperitoneal exposure was employed in 4 cases and only five operations were performed transperitoneally. Sixteen surgeons contributed cases to this series but 82 per cent of the patients were treated by 7 of the surgeons. Their respective therapeutic plans and operative techniques varied considerably.

The many different surgical procedures lend themselves to a variety of groupings, but two basic categories prevailed, as shown in table 2. In 67 of the operations the isthmus was divided while in 70 it was left intact. Nephrectomy and simple removal of calculi dominated their respective categories and accounted for 74 per cent of all the operations.

POSTOPERATIVE COMPLICATIONS

No attempt was made to evaluate transient febrile episodes and other minor disturbances that followed some of the operations. The significant complications appeared to be: urinary fistula, 6 cases, hemorrhage 3, pneumonia 3, incisional hernia 3, phlebothrombosis 3, fecal fistula 1, cerebral hemorrhage 1, and renal failure 1. Most of these sequelae were noted after removal of one half of a horseshoe kidney.

TABLE 2 *Operations on 106 patients with horseshoe kidney seen at the Mayo Clinic from 1912 through 1953*

With Division of Isthmus		Without Division of Isthmus	
Operation	Number	Operation	Number
Nephrectomy	52	Removal of calculus only	50
Nephropexy	5	Removal of calculus and pyeloplasty	5
Nephropexy and removal of calculus	3	Pyeloplasty only	3
Nephropexy, pyeloplasty and removal of calculus	2	Ureterolysis	3
		Ligation of vessels	2
Nephropexy and pyeloplasty	4	Excision of cyst	2
Division only	1	Exploration or drainage	5
Total	67	Total	70

TABLE 3 *Follow up periods for 77 living patients operated on for horseshoe kidney at the Mayo Clinic from 1912 through 1953*

Follow up Period Years	Patients
1–5	24
6–10	21
11–15	9
16–20	12
21–25	3
26–30	4
31–35	4

FOLLOW-UP

Eighteen patients are known to be dead Seventy-seven have returned for examination or have answered questionnaires The fate of the remaining 11 is unknown

Early deaths There were 2 deaths soon after nephrectomy for hydronephrosis One of these patients died of pneumonia on the seventh postoperative day and the other died in uremia on the eleventh day after operation The operative mortality rate for the entire series, based on the number of operations, was 1 5 per cent A third patient died at home 2½ months after nephrectomy for tuberculosis, and a fourth died of renal insufficiency 5½ months after bilateral calculi had been removed

Late deaths Five patients eventually died of renal insufficiency after operations for calculi but they lived for 3, 13, 15 and 29 years, respectively In all probability the operations added to the longevity of 4 of these patients

Five additional deaths which occurred 1, 2, 4, 20 and 21 years after operation were due to cardiovascular diseases and were not related to the horseshoe kidney or the operations

Four other patients died 3, 4, 5 and 26 years after operations for calculi but no accurate details could be obtained regarding their terminal illnesses

Living patients The average interval between operation and last report on 77 patients was 11 5 years (table 3) Fifty-six patients were in excellent health and

21 were ailing. Nine of the ailing had chronic renal disease (calculi or pyelonephritis or both), 7 had no urologic troubles but were incapacitated by cardiovascular disease (4 cases), peptic ulcer (2 cases) or herniated intervertebral disk (1 case), and 5 complained of vague pains which were difficult to evaluate.

General results. Of the 95 traced patients, 56 had no further complaints, 7 were relieved of all renal symptoms but were troubled by unrelated ailments, 5 had urologic relief but died 1 to 21 years later of cardiovascular disturbances, and 4 eventually died of renal insufficiency but survived for 13 to 29 years after the removal of calculi. It would appear, therefore, that at least 75 per cent of the patients derived significant benefit from the surgical treatment of their horseshoe kidneys.

Since it is most unlikely that all of the procedures noted in table 2 have the same potential values or the same inherent risks, they have been subjected to further critical appraisal, as presented in the following sections.

NEPHRECTOMY

Removal of one half of a horseshoe kidney warrants special consideration, not only because it promises to continue to be the most common operation but also because it appears to be fraught with some of the most disconcerting complications.

Indications for the 52 nephrectomies in this series were: hydronephrosis alone, 21 cases, calculi (with or without hydronephrosis) 18, tuberculosis 5, postoperative urinary fistula 6, postoperative hemorrhage 1, and pain only 1. These were primary procedures in only 37 cases; in the others, one to three operations had been performed previously.

Hemorrhage and fistula formation appear to be the greatest hazards of nephrectomy for horseshoe kidney. Thus, in this series, 3 patients had excessive postoperative bleeding. In 1 of these the responsible vessels in the lower pole of the remaining kidney were ligated 5 hours after the original operation and the patient recovered. In the other 2 the hemorrhage was complicated further by fatal uremia and fulminating pneumonia. In 2 instances there was difficulty controlling bleeding during the operation and hemostats were left on the vessels. These were removed in 48 hours in 1 case and after 5 days in the other with no subsequent hemorrhage.

In 5 cases the so-called nephrectomy failed to include all of the functioning tissue on that side and persistent urinary fistulas occurred. Two of these patients had undergone the incomplete nephrectomy elsewhere and 3 were operated on at the clinic. In 2 of these cases even the "repeat nephrectomy" was too conservative, for the fistulas persisted. In the other 3, the patients were cured promptly when care was taken to remove the isthmus as well as the remaining lower pole. For example:

Case 1. A man, aged 39 years, had marked left hydronephrosis and numerous small renal calculi (fig. 1*a*). A large left renal mass was removed but a portion of the lower pole was left in situ, as demonstrated by clusters of remaining calculi (fig. 1*b*). A urinary fistula persisted even after more stones had been

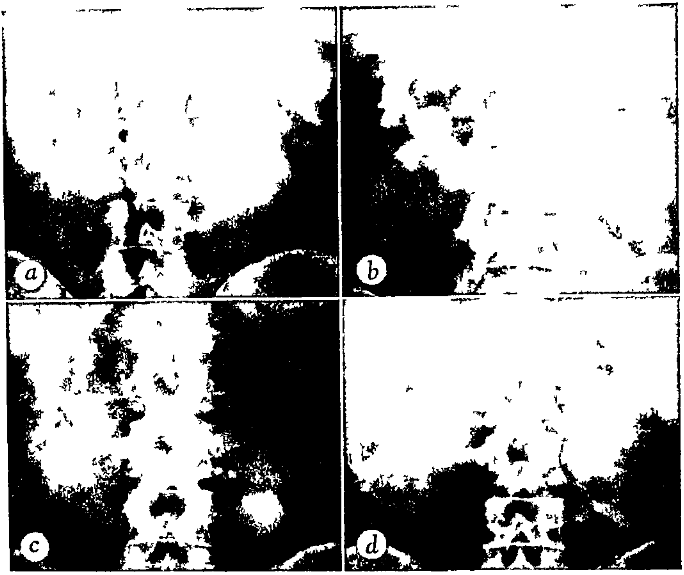

FIG 1 Incomplete initial nephrectomy *a* Preoperative excretory urogram showing advanced hydronephrosis and multiple calculi in left half of horseshoe kidney *b*, Excretory urogram after removal of bulk of left kidney Note remaining stone bearing calyces to left of vertebrae *c*, Excretory urogram after additional calculi were removed Note functioning hydrocalyx in stump of left kidney *d*, Excretory urogram after isthmus and residual portion of left kidney were excised

evacuated Functioning tissue was still present on the left (fig 1*c*) After the isthmus and this residual segment of left kidney were removed the patient had no further trouble (fig 1*d*)

Another urinary fistula that followed simple renal exploration was cured by the first attempt at nephrectomy Two additional urinary fistulas were noted after nephrectomy for tuberculosis but both healed eventually without further surgical treatment There was 1 fecal fistula after a left nephrectomy but this healed spontaneously

The technique for division of the isthmus has been reiterated throughout the literature with many personal modifications Since the isthmus can vary from a fibrous band to a broad zone of functioning cortex no one method of symphysiotomy is likely to suffice Thorough orientation regarding the nature and extent of the isthmus and careful identification of all of the anomalous blood vessels seem to be much more important than elaborate methods of suturing the remaining cortex Accurate preoperative pyelographic studies are necessary when delineation of the separate calyceal system is attempted, for many of the pelvic ramifications in the isthmus are not apparent even after the kidney has been freed

To insure success and avoid troublesome complications removal of one half of a horseshoe kidney should include excision of all cortical tissue to the adjacent pole of the remaining kidney rather than simple division at a convenient level. If the isthmus cannot be freed easily, subcapsular enucleation over the great vessels will simplify the procedure.

Subsequent excessive bleeding usually comes from the cut surface of the remaining kidney. It is imperative, therefore, that hemostasis be complete in this area. Simple mattress sutures tied over pads of fat usually suffice. Occasionally the isthmus has a separate blood supply which can be ligated. One must remember, however, that the entire blood supply to both segments of the horseshoe kidney may enter via the isthmus. Meticulous study of the entire vascular pattern is mandatory if catastrophes are to be averted. In the course of two operations in this series the surgeon abandoned his original plan to divide the isthmus because of peculiarities in the blood supply.

The large, ill-defined isthmus that extends well beyond the midline has probably been the greatest pitfall. There is reason to suspect that these can be managed more accurately by transperitoneal exposure despite the continued popularity of incisions confined to the flank.

CALCULI

More than 60 per cent of the patients in this series had nephrolithiasis. Although 18 nephrectomies were performed, conservative measures were employed in 47 cases. Unfortunately, the treatment of many of these patients antedated the appreciation of metabolic disturbances, ureteropelvic obstruction and some of the other factors in the etiology of calculi. (Our first case of hyperparathyroidism associated with horseshoe kidney was diagnosed in 1954.)

Thirty-eight patients had 50 simple pyelolithotomies or nephrolithotomies on 45 kidneys. There were 22 known recurrences in 19 patients. Five of the recurrent calculi were removed at the clinic and 2 patients had subsequent operations elsewhere. In this group the average postoperative follow-up period was 10 years. Seventeen of the 38 patients eventually claimed to be enjoying excellent health without further recurrences. Six were alive but uremic when last heard from. Nine patients died (4 of renal insufficiency, 2 of cardiovascular disease and 3 of unknown causes). The fate of the remaining 6 patients is unknown.

On the other hand, 9 patients had 10 kidneys treated by pyelolithotomy combined with pyeloplasty or nephropexy or both. There have been 2 known recurrences. Both of these followed pyelolithotomy and pyeloplasty without symphysiotomy and nephropexy. In 1 case all of the additional stones passed spontaneously or were extracted cystoscopically during the first 2 months after operation and there have been no recurrences since. It is possible that these may have been minute calculi that escaped removal at the original operation. The other patient eventually underwent a pyelolithotomy elsewhere. All of the 9 patients in this group are living 1 to 16 years after operation with an average follow-up period of 4.5 years. Two patients have hypertension but no urologic complaints. The others are asymptomatic.

It is regrettable that these two groups of patients are not comparable in size and have not been followed for similar periods It is noteworthy, however, that most recurrent calculi in both groups manifested themselves within 12 months after the original operation

The striking difference in results in these two groups is more likely due to improved renal drainage than to numerical variations Recurrence of calculi followed 44 per cent of the simple pyelolithotomies and nephrolithotomies and plagued 50 per cent of the patients who received such treatment Recurrences were reduced to 20 per cent when more efficient drainage of the renal pelvis was provided

HYDRONEPHROSIS

Hydronephrosis undoubtedly is the greatest single menace to horseshoe kidneys In 21 cases one of the fused kidneys had to be removed because of far-advanced hydronephrosis without calculi In 19 cases an attempt was made to correct the obstruction Four of the patients required operations on both kidneys The 23 conservative procedures included ligation of vessels only, 1 case, ureterolysis only 2, symphysiotomy and nephropexy 6, pyeloplasty without symphysiotomy 8, and symphysiotomy, pyeloplasty and nephropexy 6

Ligation of vessels There was no follow-up in the case in which this procedure was performed It is most unlikely that ligation of vessels alone holds much promise for success in most instances

Ureterolysis Fibrous tissue was excised from the ureteropelvic region in 1 case and both ureters were freed from an inflammatory presacral mass in the other There was dramatic improvement in both cases but these were unique situations and probably should not be compared with more conventional problems

Nephropexy Six patients had symphysiotomy and unilateral nephropexy Four had excellent results and were well 3, 5, 8 and 12 years later The fact that 2 have failed to show recurrent renal calculi is further proof of the success of the procedure In 2 cases the hydronephrosis became worse One of these kidneys eventually had to be removed

Pyeloplasty In the 8 pyeloplasties performed without division of the isthmus three techniques were employed The first technique, a Foley Y-plasty, was used in 1 case, with disappearance of all dilatation The second technique, reimplantation of the ureter, was used in 2 patients, 1 of whom improved and the other became worse The third technique, creation of another communication between the ureter and the dependent portion of the pelvis, was used in 5 patients, 4 of whom showed marked improvement while the fifth had disappointing results The 6 patients with good results have been followed for 1 to 16 years

Pyeloplasty and nephropexy Six patients had combined symphysiotomy, pyeloplasty and nephropexy Three of these were greatly improved after a Foley Y-plasty Two required subsequent nephrectomy after reimplantations of the ureter The sixth patient underwent creation of a new stoma between the ureter and the pelvis and had an excellent result The 4 patients with good results have remained asymptomatic for 2 to 4 years after operation

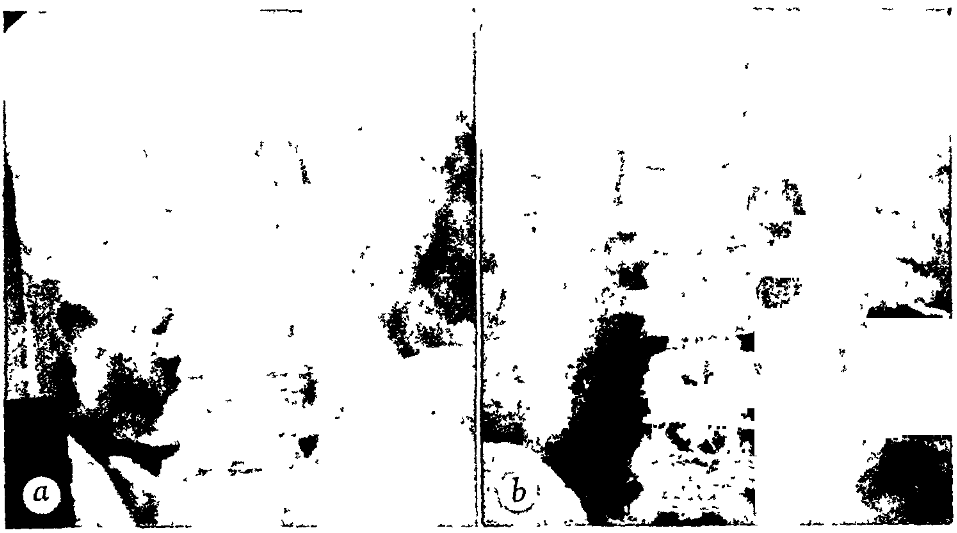

FIG. 2. *a*, Preoperative excretory urogram. *b*, Excretory urogram 3 years after symphysiotomy and left caliectomy, pyeloplasty and nephropexy.

It is noteworthy that 3 of the 4 failures subsequent to pyeloplasty followed reimplantation of the ureter and that all 4 of the patients with a Foley Y-plasty had gratifying results. Unfortunately, there are insufficient cases for adequate comparison of similar procedures with and without symphysiotomy. It may be significant, however, that calculi recurred only when the isthmus was left intact.

This small group of cases lacks statistical significance but it demonstrates several cardinal facts. Correction of hydronephrosis in horseshoe kidneys need not be stereotyped but requires careful evaluation of all possible causes of obstruction. If there is any doubt about the role of the isthmus, it had best be divided or resected. If the ureteropelvic juncture is dependent and funnel-shaped simple nephropexy will probably suffice. If there is high insertion of the ureter, some dependable type of pyeloplasty is mandatory. Furthermore, the surgical adjuncts which are employed in nonfused kidneys can be adapted advantageously to horseshoe kidneys. For example:

Case 2. A man, aged 42 years, had pain in the left flank and was found to have hydronephrosis but good function in the left half of a horseshoe kidney (fig. 2*a*). There were calcium oxalate calculi in one of the lower calyces. The isthmus was divided, the lower calyx was removed, pyeloplasty was performed and the kidney was sutured in a more nearly normal position. All discomfort disappeared promptly. Three years later the left kidney was essentially normal and there has been no recurrence of the stones (fig. 2*b*).

OPERATIONS FOR PAIN ONLY

Five of the 106 patients had no pathologic changes in their kidneys and were operated on solely for the relief of pain. The following operations were performed: symphysiotomy and nephropexy, 2 cases, symphysiotomy alone 1, ureterolysis 1, and nephrectomy 1. The kidney that was removed proved to be entirely normal.

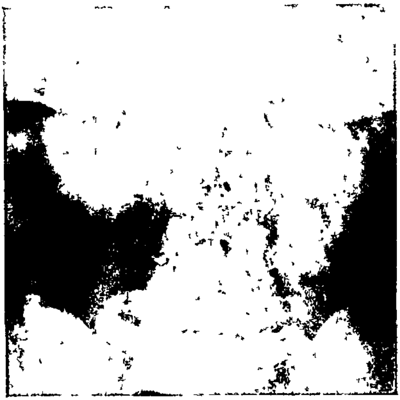

FIG. 3. Excretory urogram 33 years after symphysiotomy and right nephropexy.

Nevertheless, this was the only patient who was relieved. The others continued to have the same discomfort. For example:

Case 3. A woman had symphysiotomy and right nephropexy in 1917 at the age of 27 because of vague abdominal discomfort. Thirty-three years later she had similar pain and the upper part of her urinary tract appeared normal except for malrotation of the kidneys (fig. 3).

Guiterrez made a notable contribution when he postulated and elaborated on the so-called horseshoe kidney syndrome. But identification of these rare individuals is a painstaking process of diagnosis by exclusion.

Although much has been written regarding symptom complexes attributable to the fusion alone, there are astonishingly few well-documented examples in the literature. Most of the patients who have been relieved of pain by symphysiotomy and unilateral or bilateral nephropexy had some degree of pyelectasis, calculosis or infection. It becomes exceedingly difficult to evaluate the role of the fusion per se in the production of pain when one considers the number of patients who have obvious pyelectasis of their horseshoe kidneys but no discomfort.

Most operations on horseshoe kidneys performed solely for the relief of pain seem to be doomed to failure unless the candidates for such procedures are selected with extreme caution.

SUMMARY AND CONCLUSIONS

One hundred six cases of horseshoe kidney treated surgically at the Mayo Clinic from 1912 through 1953 were reviewed. The consolidated experiences at one institution, as disclosed in this review, are offered as further evidence to support the impressions and convictions of many independent authors.

It was observed that approximately 25 per cent of the horseshoe kidneys that were diagnosed clinically required surgical treatment. Eighty-seven per cent of the patients had calculi or hydronephrosis or both, and nearly 40 per cent had to have more than one operation. A great variety of procedures was employed. More than 75 per cent of the patients eventually had significant improvement.

The operative mortality rate, based on 137 procedures, was 1.5 per cent. Most of the serious complications followed nephrectomy. Postoperative hemorrhage and urinary fistula were the greatest problems. Meticulous attention to the anomalous renal blood supply and removal of the isthmus as well as the diseased half of the kidney will prevent these sequelae.

Forty-four per cent of the simple pyelolithotomies and nephrolithotomies were followed by recurrence of the stones. When these operations were combined with procedures designed to improve drainage of the renal pelvis the recurrence of calculi dropped to 20 per cent.

Hydronephrosis due to obstruction at or near the ureteropelvic juncture is the most common abnormality in horseshoe kidney. Many different operations are capable of relieving such obstruction but each case must be appraised carefully and thoroughly. When in doubt, the combination of symphysiotomy, pyeloplasty and nephropexy is the most dependable.

Operations solely for relief of pain are usually unsuccessful and are seldom indicated.

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UNILATERAL RENAL PAPILLARY NECROSIS

J. C. SARGENT* AND J. W. SARGENT

Renal papillary necrosis, variously referred to as necrotizing renal papillitis, necrotizing pyelonephritis, medullary necrosis, papillitis necrotans renalis, etc., is not a rare or even uncommon condition. It is, however, most often seen at the autopsy table. It is almost invariably bilateral and only rarely is the diagnosis made or even suspected before death. At autopsy, the kidneys present a bizarre but characteristic picture of ischemic necrosis of the apical portion of the renal pyramids. All stages may be seen from simple necrosis to complete dissolution and sloughing of the renal papillae.

Since this condition was first described by vonFriedreich[1] in 1877 many cases have been reported. The case described by vonFriedreich was associated with hydronephrosis. Gunther[2] was the first to emphasize the relationship of renal papillary necrosis to diabetes, and most of the cases reported subsequently have been found in diabetics. Except for a very rare case apparently caused by retrograde injection of a strong contrast medium[3] and one case occurring postpartum,[4] all the cases reported have been associated with either diabetes or urinary tract obstruction. Edmondson's series[5] indicates 60 per cent occurring in diabetes and 40 per cent with obstructive uropathies.

Clinically the condition must be thought of in any severe diabetic with an uncontrollable urinary tract infection. Harrison and Bailey[6] have emphasized the frequency of asymptomatic urinary tract infections in diabetics. In the event that such an infection does not respond to treatment or suddenly becomes more severe in spite of treatment, renal papillary necrosis must be considered. Likewise, diabetic "coma" which is out of all proportion to the degree of diabetes may, in fact, be uremic coma due to extensive renal papillary necrosis. Occasionally the condition will be brought to light by typical renal colic due to ureteral obstruction caused by a sloughed renal papilla. Fairly intact papillae may even be passed in the voided urine and identified histologically.

Excretory urograms may reveal negative shadows of sloughed renal papillae floating freely in the renal pelvis. Braasch and Emmett[7] describe the characteristic urographic findings as the result of erosion and destruction of the renal papillae and emphasize the similarities between this and renal tuberculosis or advanced nontuberculous pyelonephritis.

Read at annual meeting, North Central Section of American Urological Association, Detroit, Mich., October 7–9, 1954.

* Deceased.

[1] Referred to by Edmondson.[5]

[2] Gunther, G. W.: Die Papillennekrosen der Niere bei Diabetes. Munch. med. Wchnschr., 84: 1695, 1937.

[3] Eskelund, V.: Necrosis of renal papillae following retrograde pyelography. Acta Radiol., 26: 548, 1945. (Abstracted in J.A.M.A., 130: 1192, 1946.)

[4] [illegible] is of kidneys. Lancet, 2: 187–189, 1937.

[illegible] and Evans, N.: Necrosis of renal papillae and acute [illegible] rch. Int. Med., 79: 148–175, 1947.

[illegible] Significance of necrotizing pyelonephritis in diabetes [illegible]

[7] Braasch, W. F. and Emmett, J. L.: Clinical Urography. Philadelphia: W. B. Saunders Co., 1951.

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kidney. In all there have been reported only five clear-cut cases of unilateral papillary necrosis, treated by nephrectomy with apparent excellent results. The authors wish to add another case.

CASE REPORT

Mrs. A. D., a 61 year old white, married woman, was a known diabetic for many years who had not co-operated in efforts to control her diabetes. On May 23, 1954 she experienced sudden, severe, left upper quadrant colic followed by nausea and vomiting. She became progressively agitated, irrational and finally stuporous, and 2 days later was hospitalized in diabetic coma. Positive findings on admission included: Temperature 99.4F, pulse 100 and weak, respirations 30, blood pressure 190/110. Her abdomen was distended and tympanitic with hyperactive bowel sounds. There was definite left costovertebral angle tenderness. Rales were noted in the bases of both lungs. A funduscopic examination was negative.

Laboratory studies indicated blood sugar of 446 mg. per 100 cc, and CO_2 combining power 21.4 volumes per cent. A catheterized urine specimen contained albumin 3 plus, sugar 4 plus (2 per cent), acetone 2 plus, 15–20 white blood cells and no red blood cells or casts. The hemogram was normal except for a white count of 17,800 with 36 per cent stab forms and 45 per cent segmented neutrophils.

During the first 16 days of hospitalization she was treated medically with insulin and many antibiotics. She was very difficult to stabilize and during this time she had a convulsion, thrombophlebitis, and a hypoglycemic reaction as complications. A urologic consultation was then sought because of persistent pyuria.

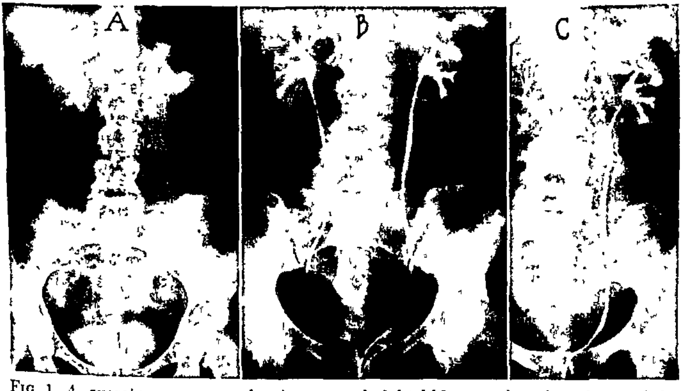

FIG. 1. *A*, excretory urogram showing normal right kidney and no function on left. *B*, bilateral retrograde pyelograms. Right kidney normal. Deformities of middle and upper calyces of left kidney suggest papillary necrosis. *C*, left retrograde pyelogram showing greater detail. Note erosion of middle calyx, infiltration of contrast medium into calyx above, and complete separation of renal papilla in calyx medial to this.

An excretory urogram (fig. 1, *A*) revealed the right upper tract to be normal. There was no function on the left even in the delayed films.

Catheters were passed up each ureter with ease. Urine obtained from the right renal pelvis was microscopically negative and revealed no organisms on culture. No urine was obtained from the left, but washings of the left renal pelvis revealed pus cells. The washings failed to grow any organisms on culture, however. Culture of the bladder urine revealed E. coli and Pseudomonas. Specimens from the kidneys and bladder were submitted for complete acid-fast studies which proved subsequently to be negative.

Bilateral retrograde pyelograms again revealed the right side to be normal (fig. 1, *B*). The left kidney revealed a bizarre deformity of the middle and upper calyces. Another film of better detail (fig. 1, *C*) showed a large eroded area in the middle calyx suggesting complete separation and sloughing of the papilla. The calyx immediately above this showed infiltration of contrast medium irregularly into the papilla suggesting necrosis and partial separation of the papilla. Medial to this another calyx showed a complete separation of the papilla which appeared to be floating freely.

A diagnosis of unilateral renal papillary necrosis was made on the basis of these findings. The patient was then watched carefully for another 2 weeks during which time her temperature gradually returned to normal and the diabetes was under control. Heavy pyuria persisted, however, in spite of heroic doses of every conceivable antibiotic. After 2 weeks an excretory urogram was repeated, and when this again revealed a complete absence of function in the left kidney it was felt that nephrectomy was indicated.

Nephrectomy was performed uneventfully on June 25, 1954. Except for a very mild wound infection her convalescence was uneventful and she was dismissed on the twelfth postoperative day in excellent condition. Her urine was free from sugar and had only 6 to 8 pus cells per high powered field in the centrifuged speci-

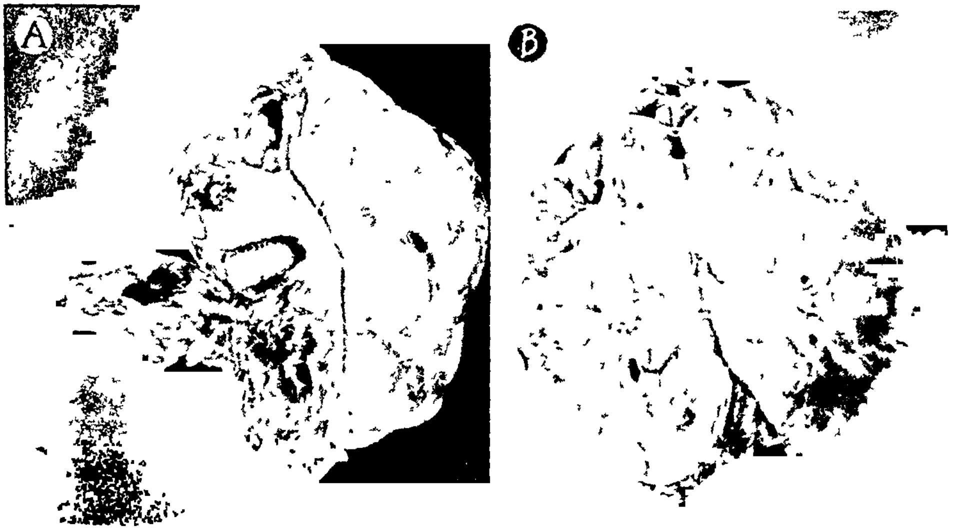

FIG. 2 *A*, gross specimen (left kidney) with adherent capsule reflected. *B*, left kidney transected. Note several pale, necrotic renal papillae

men Her diabetes was readily controlled with 45 units of insulin daily Nine months postoperatively she was in excellent health Her urine was entirely normal microscopically, free from albumin or sugar, and negative to the Gram stain

The surgical specimen is of particular interest Grossly (fig 2, *A*) the thickened capsule peeled with difficulty and revealed the kidney surface lumpy and irregular with fine granular pitting and large, pale, nodular areas

Upon transecting the kidney (fig 2, *B*) one sees the parenchyma to be quite pale and several pale necrotic papillae can be seen Figure 3 under higher power reveals a typical papilla from which the following microscopic studies were obtained

Figure 4 is a low powered view of the entire pyramid and we see grossly the area of necrosis sharply limited to the renal papilla, an inflammatory reactive

FIG 3 Enlargement of figure 2, *B* Note typical necrotic papilla

FIG 4 Low power of renal pyramid seen in figure 3 Note necrotic papilla with adjacent zone of hyperemia

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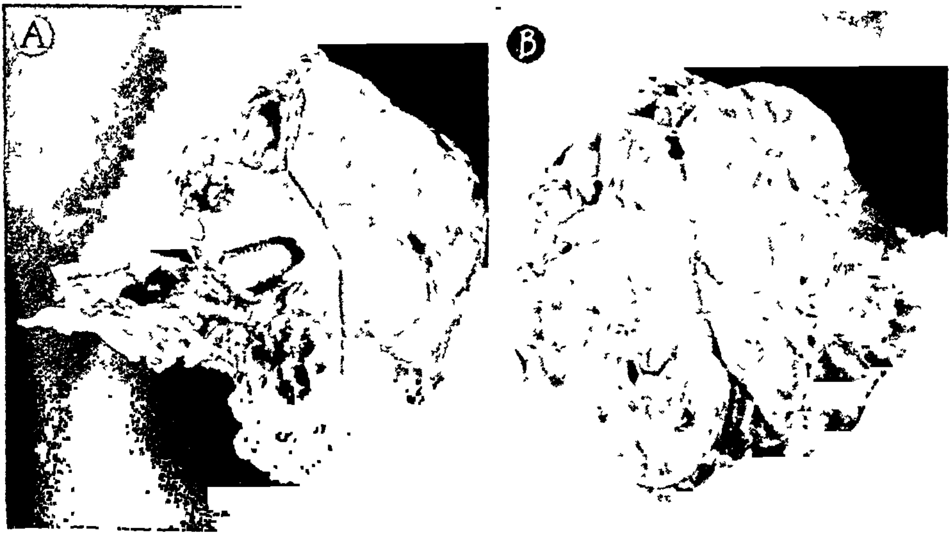

FIG. 2. *A*, gross specimen (left kidney) with adherent capsule reflected. *B*, left kidney transected. Note several pale, necrotic renal papillae.

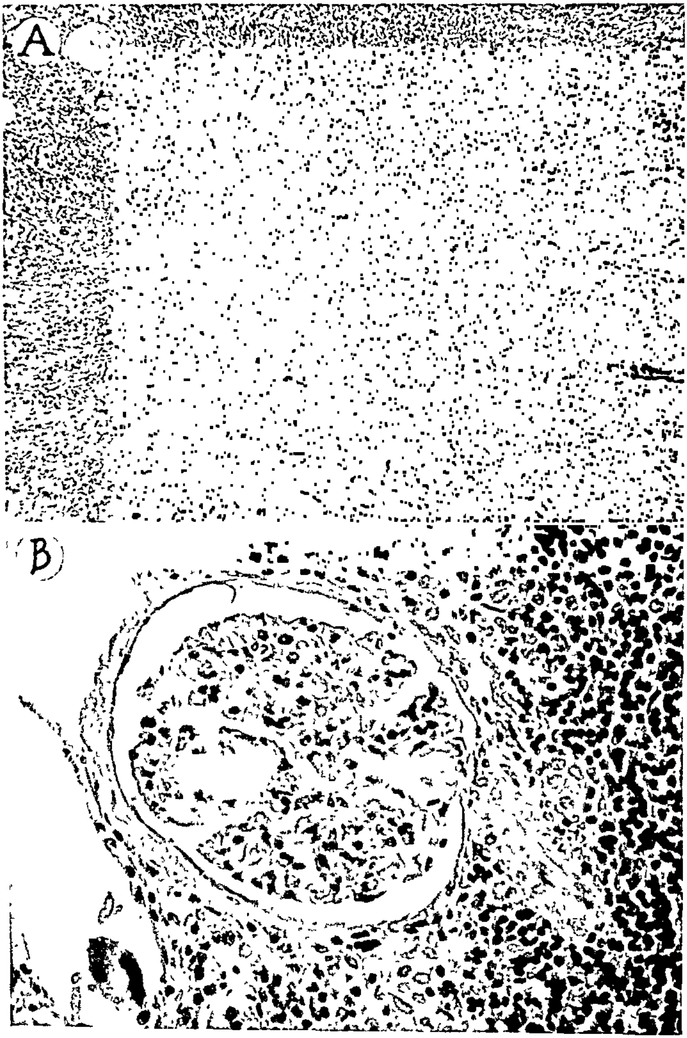

FIG. 6. *A*, high [illegible] ramid seen in figure 4. Marked pyelonephritis. Several [illegible] -Wilson's disease. *B*, glomerulus showing Kimmelsteil-Wilson's disease.

zone, and peripherally rather normal medullary tissue. A high power view (fig. 5, *A*) of the necrotic zone and (fig. 5, *B*) of the reactive zone reveals marked hyperemia and inflammation which is somewhat unusual in the marked preponderance of plasma cells. Figure 6, *A* taken at the base of the pyramid shows marked pyelonephritis and in some areas glomeruli. Some of the glomeruli show characteristic Kimmielsteil and Wilson's disease (fig. 6, *B*).

DISCUSSION

It is at present impossible to understand why such a disease process which is so characteristically bilateral should be so clearly limited to one kidney. Suffice it to say that the condition does exist and should always be borne in mind whenever one sees a diabetic patient with an uncontrollable urinary tract infection.

SUMMARY

A case is presented of unilateral renal papillary necrosis diagnosed clinically and treated by nephrectomy with apparently satisfactory results.

324 E. Wisconsin Ave., Milwaukee 2, Wis.

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RENAL VEIN THROMBOSIS IN THE NEWBORN

B A SMITH, JR

Urologic awareness of the syndrome of renal vein thrombosis in the newborn has been wanting No reference devoted to it has appeared in the recent urologic literature[1, 2, 3, 4, 5] until August 1954[6] The pediatric literature has a number of articles upon the subject, but it behooves the urologist to be familiar with the disease

McClelland and Hughes[7] state, "thrombosis of the renal veins in infants causes a rarely diagnosed syndrome characterized by sudden onset of hematuria or anuria, shock, and the appearance of palpable lateral abdominal masses in an infant usually suffering from dehydration as a result of a severe diarrheal disorder " If this sentence is remembered, the clinical diagnosis will be made more frequently and the prognosis improved

CASE REPORT

M S , a white male infant, was hospitalized by Dr Harold Hermann January 24, 1954 at the age of 13 days Birth history was normal Anorexia and then projectile vomiting began 3 days before admission Stools were frequent, small, and soft without melena Onset of acute colicky abdominal pain was noted about 9 00 p m , January 23, 1954, and when first seen by Dr Hermann a mass in the right side of the abdomen was present Temperature was 97 4F The baby was dehydrated, eyes were sunken, and the facies drawn and ashen gray There was a tender, firm mass the size of a baby's fist in the right side of the abdomen No blood was noted on rectal examination Hemoglobin upon admission was 21 6 gm per cent, white blood cells numbered 23,900/cu mm with 74 per cent polymorphonuclear leukocytes The urine was pink and contained 2 plus albumin, many white blood cells and red blood cells were present upon microscopic examination The patient was hydrated and transfused, and when stabilized in regard to shock, barium enema excluded intussusception

January 25, the hemoglobin had fallen to 15 9 gm per cent, and leukocytes numbered 39,800/cu mm An excretory urogram was made but no definite excretion of dye was seen and renal shadows could not be outlined When seen by me that evening the mass was as described, the abdomen was distended, and

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Read at annual meeting, North Central Section of American Urological Association, Detroit, Mich October 7–9, 1954

[1] Aschner, P W Thrombosis and thrombophlebitis of the renal vein J Urol , **17:** 309 327, 1927

[2] Hepler, A B Thrombosis of the renal veins J Urol , **31**· 527–546, 1934

[3] Melick, W F and Vitt, A E Thrombosis of the renal vein J Urol , **51** 587 596, 1944

[4] Abeshouse, B S Thrombosis and thrombophlebitis of the renal veins Urol & Cutan Rev , **49** 661–675, 1945

[5] Regan F C and Crabtree, E G Renal infarction a clinical and possible surgical entity J Urol , **59** 981–1014, 1948

[6] Stevens, R C and Tomsykoski, A J Thrombosis of the inferior vena cava and renal veins with hemorrhagic renal infarction J Urol , **72** 120–126, 1954

[7] McClelland, C Q and Hughes, J P Thrombosis of the renal vein in infants J Pediat , **36** 214–227, 1950

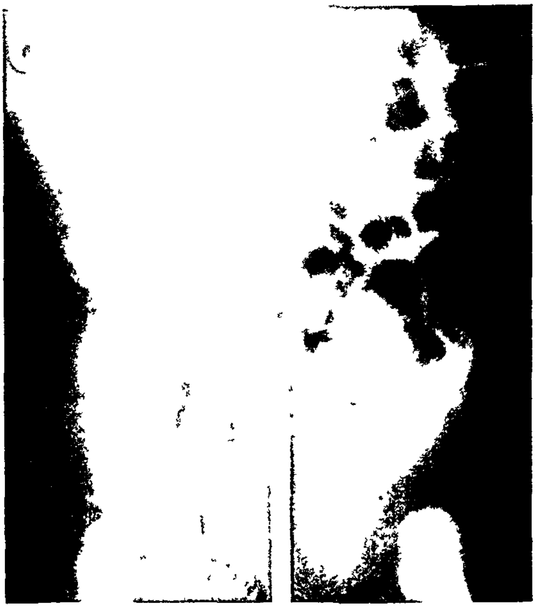

FIG. 1. Right retrograde pyelogram. Note blotchy extravasation of dye through mushy lower pole and medial displacement of ureter and bowel.

abdominal veins were prominent. There was opisthotonos but the fontanelle did not bulge. Temperature was 102.6F. A diagnosis of right renal vein thrombosis with possible vena caval thrombosis was proposed. Antibiotics were begun.

January 26, 1954 the abdomen was softer, the mass questionably larger, and the distention of the abdominal veins had disappeared. The opisthotonos was more marked. Hemoglobin was 9.5 gm. per cent and blood urea nitrogen was 65 mg. per cent. Cystoscopy without anesthesia revealed pink urine in the bladder. The left ureteral orifice spurted regularly and the jets were tinged with a trace of indigo carmine. A little bloody fluid escaped from the right ureter upon passage of a catheter. Another x-ray showed more displacement of the bowel toward the midline by the right abdominal mass than previously. The retrograde pyelo-ureterogram showed blotchy extravasation of dye through parenchyma and medial displacement of the ureter (fig. 1). Following the injection of dye, the patient appeared to be in collapse and the renal mass seemed larger. Right renal washings showed hemolytic paracolon bacillus upon culture. Blood culture was not taken. Impairment of left renal function was presumed to be on the basis of shock and anoxia (lower nephron nephrosis).

Following stabilization of the child's condition by the further administration of oxygen and blood, nephrectomy was done through a right lumbar incision with intratracheal anesthesia. The kidney was markedly enlarged, purplish-red, tense yet soft, and there were small subcapsular hematomas and perinephric ecchymosis. No thrombus was palpable in the vena cava. Immediately after operation, marked improvement took place in the baby and several of us noted that his anxious facies became peaceful, and the opisthotonos much less. Convalescence was smooth and at the time of discharge, February 6, 1954, the urine was negative on microscopic and cultural examination, and the blood urea

FIG. 2. Gross specimen. Black and white prints show kidney in massive thrombosis as a black glob with little contrast. This is apparent in other reports also. The sectioned kidney reproduced even more poorly.

nitrogen was 16 mg. per cent. When checked by Dr. Hermann in August 1954 the boy was developing normally.

The kidney weighed 32 gm. (normal 15) and was darkly hemorrhagic with obliteration of the markings (fig. 2). On microscopic examination there was almost complete obliteration of all architectural details because of hemorrhagic necrosis. There was fresh laminated thrombus completely occluding the renal vein and its principal branches (fig. 3, *A*). Inflammatory changes were inconspicuous; the arteries were normal. Gram stain of the tissue showed large numbers of pleomorphic gram-negative rods, scattered and in clusters in the tissue (because of necrosis, exact relation to type of tissue not determined) and in the thrombus (fig. 3, *B*).

COMMENTS

The condition is uncommon, but McClelland and Hughes found, in 328 autopsies on infants, 3 cases among the 31 deaths due to diarrhea. Barenberg et al.[8] reported 5 cases in 25 autopsies during an epidemic of diarrhea in the newborn. The syndrome occurs in children up to 3 years of age, but is quite uncommon beyond the age of 1 month. It may occur rarely in the postpartum mother. There is no predilection as to sex or side of involvement. Fifty per cent of the cases are bilateral with a very grave prognosis although Fallon[9] reported a re-

[8] Barenberg, L. H., Greenstein, N. M., Levy, W. and Rosenbluth, S. B.: Renal thrombosis with infarction complicating diarrhea of the newborn. Am. J. Dis. Child., **62**: 362–372, 1941.

[9] Fallon, M. L.: Renal venous thrombosis in the newborn. Arch. Dis. Child., **24**: 125–128, 1949.

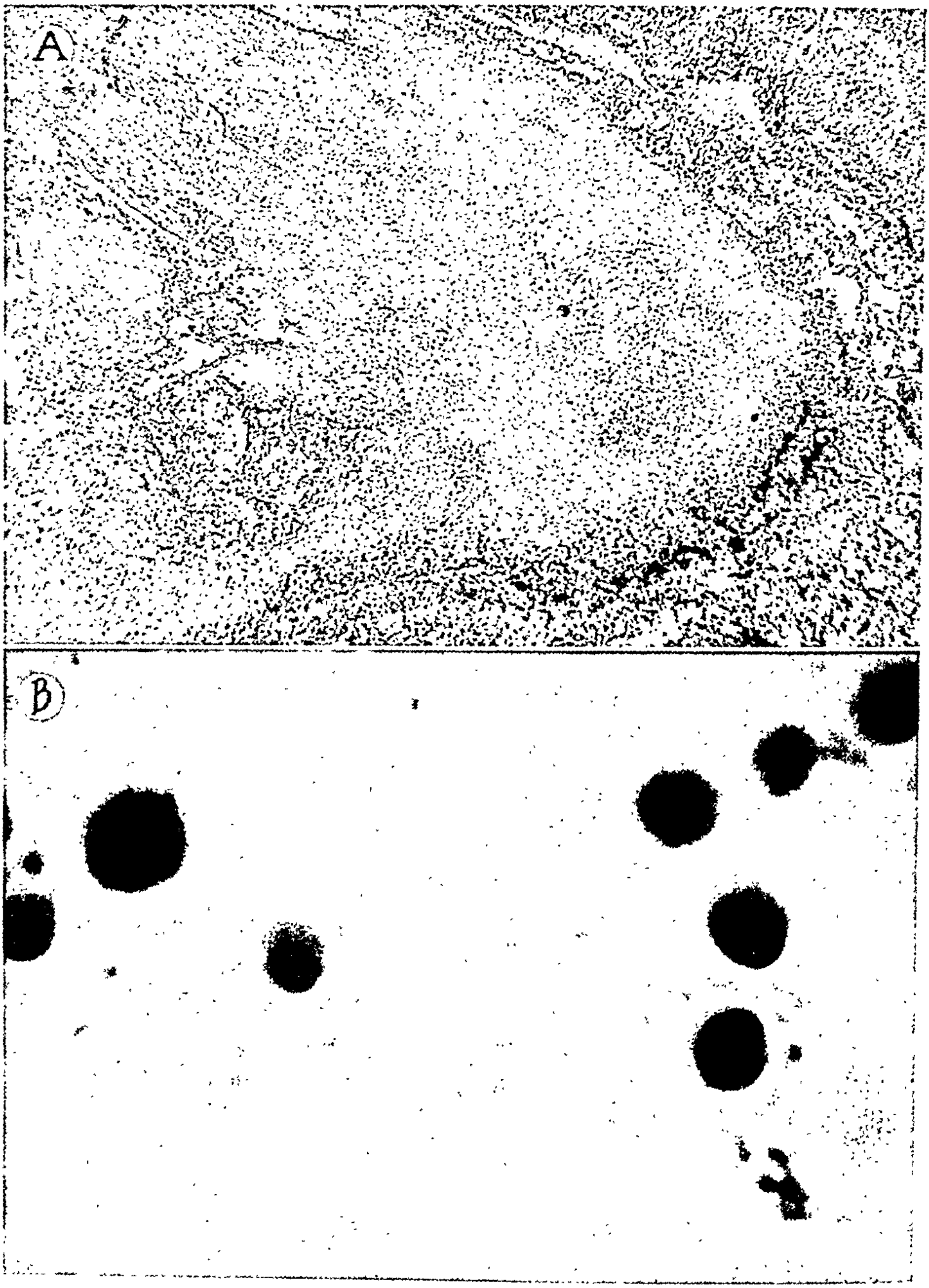

FIG. 3. *A*, portion of thrombus of one of veins at hilus. *B*, oil immersion field of thrombus (*A*) showing bacilli. (Counter stain of methylene blue. Gram stain did not photograph well.)

covery. The mortality in unilateral cases has been estimated at 95 per cent without surgery and 25 per cent with surgery. Death usually occurs within a very few days after appearance of abdominal mass, unilateral or bilateral.

PATHOGENESIS AND ETIOLOGY

Primary thrombosis may occur with or without infarction depending upon degree and rate of thrombosis. Massive infarction may occur without thrombosis.

Infarction may occur secondary to pyelonephritis with or without thrombosis, and Hepler[9] believed all cases were of this origin, but most believe this to be very uncommon. Secondary or ascending thrombosis does not enter the scope of this paper.

Certain factors are common to most of the cases. Infection in the form of enterocolitis, omphalitis, skin infections (forceps lacerations), pneumonia, pharyngitis, and otitis media usually antedates the onset. Dehydration due to diarrhea, vomiting, fever, and feeding problems (thrush) is present, superimposed upon the physiologic dehydration of the newborn (6–10 per cent weight loss). This promotes further concentration of the normally polycythemic status of the newborn. Venous and capillary pressures are normally low in the neonatal period. Bed rest increases thromboplastin. These factors promote sludging. The double capillary network of the kidney is believed to be the reason for the predominate occurrence of thrombosis of renal veins although independent or associated thrombosis of meningeal veins is not uncommon. Toxic damage to the walls of the renal veins has been proposed as a predisposing factor[10, 11, 12] but is not generally accepted. Prothrombin is normally low in the newborn so that if thrombosis occurs, the associated hemorrhage is greater and swelling further decreases the blood flow promoting further thrombus formation.[13] Congenital abnormality of the renal veins has been proposed as a possible etiologic factor.[14]

Sandblom[15] states there is a group in which no infectious or dehydrative process antedates the onset of thrombosis and Zeulzer et al[13] and Warren et al[14] describe cases believed to have occurred in utero.

PATHOLOGY

There is little agreement as to the veins first involved. Campbell[16] believes the peripheral and glomerular vessels are first involved. General opinion accepts thrombosis in the small or medium sized veins with appearance of symptoms when the main vein is involved.[15, 16] Two of Barenberg's cases had thrombi only in the main veins. Depending upon the duration and completeness of the process, canalization may occur.

With massive infarction, the kidney is enlarged two or three times normal size. It is reddish purple in color, soft and mushy, and may have subcapsular hemorrhages with perirenal ecchymosis or hematoma. Regan and Crabtree[5] state most of the clots are infected. Finklestein[17], and Czerny and Moser[18] found organisms in the thrombi. Barenberg et al did not find bacteria in the thrombi or in tissue,

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[10] Oppenheim. Quoted by Barenberg.

[11] Clatworthy, H W, Jr, Dickens, D R and McClave, C R. Renal thrombosis complicating epidemic diarrhea of the newborn. New Eng J Med, 248: 628–630, 1953.

[12] Jones, D B and Loring, W E. Glomerular thrombosis. Am J Path, 27: 841–855, 1951.

[13] Zuelzer, W W, Charles, S, Kurnetz, R, Newton, W A Jr and Fallon, R. Circulatory diseases of the kidneys in infancy and childhood. Am J Dis Child, 81: 1–46, 1951.

[14] Warren, H, Birdsong, McL and Kelley, R A. Renal vein thrombosis in infants. J A M A, 152: 700–701, 1953.

[15] Sandblom, Ph. Renal thrombosis with infarction in the newborn, two different forms. Acta paediat, 35: 160–167, 1948.

[16] Campbell, M. Clinical Pediatric Urology. Philadelphia: W B Sanders Co, 1951, pp 441–444.

[17] Finklestein. Quoted by Barenberg.

[18] Czerny and Moser. Quoted by Barenberg.

nor did Kobernick et al.[19]; most observers report no notable infectious process in the vein walls when the lesion is recent. Culture of the thrombus has been found sterile.[20] The medulla suffers most and first, but renal architecture is lost or masked by the extensive hemorrhage. Necrosis in sudden, massive infarction involves all the parenchyma except a negligible subcapsular zone.

Thrombosis of the opposite or second kidney may be of the same origin or may occur by extension by the vena cava. Adrenal infarction is a frequent companion. The uninvolved kidney *may suffer (and probably commonly does) from* so-called lower nephron nephrosis due to shock and anoxia as noted by McClelland and Hughes and Milburn.[21]

Pulmonary emboli were found by Morison[22] in 9 of 14 cases that had thrombi in the renal vein; emboli or thrombi were found in the pulmonary arteries in two of 3 cases reported by McClelland and Hughes, and three of 4 cases described by Kobernick et al.

SYMPTOMS AND FINDINGS

Infection and dehydration are usually present. The patient appears marasmic and hematuria usually is gross. A picture of shock appears when the infarction occurs and the mass is noted. Opisthotonos has been observed, but the fontanelle is depressed. Restlessness is common. Fever is the rule. Urinalysis in massive infarction shows red blood cells, white blood cells usually (and almost always later), albumin, casts and, in most of the cultures, bacteria. Leukocytosis occurs and hemoglobin falls. Acidosis and uremia in varying degree are present.

X-rays usually show a mass and the displacement of the bowel shadows. Flecks of blood in the stool are common, and together with a right abdominal mass often prompt a barium enema to exclude intussusception. Excretory urography shows no function on the involved side, and may or may not show function on the "good" side depending upon the gas shadows of the newborn, and the renal function (lower nephron nephrosis). Retrograde pyelography shows first a tendency for the ureter only to fill because of compression of the collecting system[3, 5] by parenchymal swelling. If injection is carried further, dye extravasates through the mushy kidney in irregular collections larger than seen with the usual pyelovenous or pyelotubular extravasation, as described by Campbell.[16]

DIFFERENTIAL DIAGNOSIS

Differential diagnosis includes hemorrhage into Wilms' tumor, infected or noninfected hydronephrosis, renal dysplasia with cystic mass, unilateral or bilateral polycystic disease, renal or perinephric abscess. Retrograde pyelography should establish the diagnosis.

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TREATMENT

Preoperative therapy demands hydration, transfusion if anemia is present, balance of electrolytes, and measures to combat infection If the thrombosis is bilateral, surgery is contraindicated In unilateral thrombosis, nephrectomy should be done as soon as the diagnosis is established and the patient's condition is stable In the cases with infection, time is of great importance Lumbar incision is very satisfactory for this condition The renal vein should be severed medial to thrombus and Sandblom removed thrombotic extension from the vena cava

Following operation, improvement in the patient's condition is usually immediate and dramatic Attention is given to fluid and electrolyte balance, blood, and control of infection Anticoagulant therapy in the postoperative period to prevent extension of thrombus, new thrombus formation, and to discourage propagation of silent, small, contralateral thrombi has been suggested by a number of authors and heparin was employed by Parry[23] but was discontinued after 3 days because of wound bleeding Because hemorrhage into the kidney is so marked with massive infarction and furthermore may be a factor in extending thrombus formation,[13] anticoagulant therapy in unoperated or bilateral cases is a two edged sword

Gruneberg[24] reported in 1932 the first nephrectomy with cure to come to my attention Campbell[25] performed nephrectomy with cure in 2 cases, and first made the preoperative diagnosis in the second case Since then 9 cases have been reported[15 20 26 23 14 (2 cases) 27 28 11] with one questionable case in regard to outcome,[29] a total of 12 or 13 cases cured by nephrectomy The only case of recovery with a clinical diagnosis of bilateral thrombosis was reported by Fallon [9] Renal function gradually improved over months She questions the advisability of surgery in all unilateral cases unless infection is present The possibility of cure probably depends upon a slow rate of occlusion or accessory vessels, uninvolved

DISCUSSION

A pediatrician whose brother[20] (pathologist) had encountered a case of renal vein thrombosis cured by nephrectomy once told me he didn't want to overlook such a diagnosis I was forced to look up Campbell's writings to acquaint myself with the subject Once aware of the existence of such a condition, the rather typical history and findings made the presumptive diagnosis quite apparent The prominence of dilated veins in the abdominal wall (mentioned by others) suggested vena caval involvement but rather disappeared with decrease in distention (also noted by others). The opisthotonos was marked and proposed the question of meningismus due to cranial sinus thrombosis or encephalitis or meningitis. The normal soft fontanelle in the presence of adequate hydration was somewhat reassuring, and spinal fluid was not examined. The rate of fall in the hemoglobin was remarkable and beyond the change in hydration. The baby seemed to become "shocky" co-incident with retrograde pyelography, and the mass seemed to increase in size at that time. Retrograde pyelography in suspected renal infarction with bilateral masses would seem contraindicated. The presence of organisms in the tissue sections would explain the dramatic improvement immediately following nephrectomy. Antibiotics might control the systemic infection, but would not be expected to eradicate infection in a hemorrhagic renal mass deprived of circulation.

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SUMMARY

Renal vein thrombosis with massive infarction should be readily recognized if the condition is considered although the associated infection and prostration may mask it somewhat. The possibility of renal vein thrombosis should be anticipated in all infants with infection and dehydration, and abdominal palpation and urine inspection should be routine.

Approximately one-half of the cases will be unilateral, and three-fourths of these may be expected to survive with proper treatment.

Correction of dehydration, electrolyte imbalance, and anemia, and measures to control infection are essential.

The diagnosis may be established by retrograde pyelography, but this is contraindicated when masses are bilateral.

Treatment at this time is nephrectomy in unilateral cases, and is urgent when infection is present. Postoperative anticoagulant therapy would seem advisable.

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PROGNOSIS IN HYPERNEPHROMA: REVIEW OF THE LITERATURE AND REPORT OF 42 CASES

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It would be of the highest value to the surgeon were he able to accurately predict the outcome in his cases of parenchymal renal malignancies. Yet in the vast literature on this subject, there has not been agreement on what criteria are valuable toward this end. The urgency of the problem becomes evident from the enthusiasm with which surgeons accepted Broders' microscopic grading of tumors and Graham's criteria of malignancy of thyroid tumors.

In 1932 Hand applied Broders' grading to hypernephromas, basing it on four classes of malignancy according to cellular differentiation. In grade 1, 75–100 per cent of cells were differentiated; in grade 2, 50–75 per cent; in grade 3, 25–50 per cent; while in grade 4, 25 per cent to none were differentiated. Herbut believes that this grading is unreliable and judges prognosis on the overall impression, the gross appearance, extension beyond the capsule, invasion of renal veins, and presence or absence of metastasis.

Bell, in 149 postmortem hypernephromas, found only one metastasis from tumors less than three centimeters in diameter. He felt that ". . . small tumors (so-called adenomas) are early stages of the large growths and no certain distinction can be made between adenoma and carcinoma. . . ." In addition to these micromorphologic gradings, stages of invasion of blood vessels, as applied by Graham in Duke's classification of colon tumors, have been considered. Still, the life expectancy in different malignant tumors may vary from a few weeks to many years. Carlson and Ockerblad reported the case of a patient with unoperated hypernephroma who lived 10 years. One of our cases appeared with symptoms of 4 months' duration, was operated on and 3 months later the patient died of metastasis and recurrence. Another died 6 years postoperatively of metastasis and another 9 years after nephrectomy of metastasis. In still another, after 6 years, a lung lesion suddenly developed that lobectomy established as hypernephroma. Another patient had a solitary lesion in the humerus which was removed during the hospital admission for nephrectomy. She is alive and symptom free without evidence of disease 1 year later. Two others are living and free of evidence of disease 10 and 23 years postoperatively.

In these cases, which were ours, the degree of microscopic differentiation was virtually the same, all were larger than 5 cm. in diameter, all were predominantly clear-cell types. At surgery one had already metastasized; only the patient who died after 6 years had had demonstrable renal vein involvement at the time of nephrectomy.

GENERAL PROGNOSIS

It is generally agreed that taken as a group, the outlook for hypernephroma stastistically is poor. Reported 3-year survivals vary from 20–46 per cent; 5-year

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survivals from 11–46 per cent; and 10-year survivals from 6–22 per cent. At this clinic 22 of our patients could be followed for more than 5 years. Any immediate postoperative deaths were excluded. Of the 22 cases, eight were living after 5 years, a 36.3 per cent survival rate. Of these, one had known metastasis 6 years postoperatively. The 10-year survival rate is based on 14 cases excluding postoperative deaths. Two are living, a 14.2 per cent survival rate.

In analyzing cases reported by Adams, Melicow, Deming, Harvey, Dick, Duff and Glen, an average of 33 per cent were known to be dead in less than one year and 65 per cent in less than ten years. At our clinic, 34 cases operated on from 1922 to 1953 were analyzed as to time of death. In these, twelve had had surgery less than 5 years ago. Of these 34 cases, 20 are known to be dead, 18 dying in less than 5 years; 9 were dead in less than 1 year; 11, less than 2 years; 15, less than 3 years; 16, less than 4 years; 18, less than 5 years.

MICROMORPHOLOGY AS A CRITERION

Hand and Broders found in a total of 193 cases studied, graded according to the cell differentiation method, that the average duration of life decreased from 101.4 months in grade 1 tumors to 22.53 months in grade 4 tumors. Fifty per cent of the grade 1 tumors and 96 per cent of the grade 4 tumors were dead when the paper was written. In the literature we reviewed, the Broders' grading system was not widely used in reporting prognosis. Melicow evaluated prognosis from clear cell tumors downward to dark cell ones. Foot, Riopelle, Adams and Cahill had a similar experience. Others: Deming, Dick, Priestley and McDonald, and Kretschmer have been unable to demonstrate any significant relation between histology and prognosis. In our series, twenty-two had 5-year follow-ups. The slides were reviewed as to predominant cell type. Eighteen were largely clear cell, two were largely dark cell, and the other two were equally both types. We were unable to demonstrate any relationship to prognosis in such a small series.

TUMOR SIZE

Bell, Shakeen, Hale and Burkland, Kozall and Kirshbaum have all reported the virtual absence of metastasis in renal hypernephromas of less than 3 cm. in diameter. Priestley and MacDonald found no relation to weight of tumor and survival, but believed larger tumors had a poorer outlook due to increased chance of extension. Graham, in a study of 195 cases, states that larger tumors give a worse prognosis. Bobbitt and Harwood report 48 cases and find a 33 per cent survival with small tumors and invasion, but only 20 per cent survival if the tumor was large. In our series, 39 of 42 tumors were greater than five centimeters in diameter. Of the three small tumors, one died of metastasis 2 months postoperatively; one was alive 1 year and another 3 years after operation. Twenty of the forty larger tumors could be followed 5 years and seven were living at the end of that time.

INVASION OF VEINS AND PERIRENAL TISSUE

There is general agreement that demonstrable tumor thrombi in renal veins, or vena cava, darken the outlook. Perhaps the great diversity of reactions to tumor emboli is explained by the inherent individual reaction to the implants. There are cases where vena caval implants have been found, yet the patient may outlive by some years those with smaller tumors where no gross evidence of spread was seen. Why, when the body is probably showered with tumor cells by way of the blood stream, metastases appear late or not at all remains a mystery. In the words of Melicow, ". . . not all (tumor) emboli survive, but (some) because of favorable physiochemical biologic factors tend to form a colony . . ."

Saphir studied the fate of carcinoma emboli in the lungs of patients dying of carcinoma. He found that tumor emboli lodged in tiny end vessels and became surrounded with hyaline thrombus which in turn became organized. He found that definite loss of viability then appeared in the tumor cells and postulated that the hyaline thrombus caused their atrophy and eventual autolysis.

Mann has recently collected 2 cases, and added two of his own where spontaneous disappearance of pulmonary metastasis from hypernephroma was said to have occurred. If it is true, as is suggested by these workers, that multiple tumor emboli do not necessarily mean multiple metastases, then the removal of the hypernephroma and a solitary metastasis might increase life duration. Albrecht removed a solitary scapular metastasis and obtained a 9-year survival. Creevy found that numerous hypernephroma bone metastases were solitary and amendable to removal.

Perirenal extension in most reported series occurred with large tumors, often diagnosed late. The advocation of more radical nephrectomy by some (Foley, et al.) would seem to depend on whether ultimate death from hypernephroma was due to distant metastasis or local recurrence. Our own series had too few autopsies to provide an analysis of this factor.

However, of 23 cases available, six had renal vein or vena caval involvement. Of these, two survived 5 years (33 per cent). Seventeen cases had no demonstrable involvement and seven of these survived 5 years (41 per cent). Ten cases had perirenal extension and three of these survived for 5 years (33 per cent). Thirteen had no demonstrable extension, six lived 5 years or more (48 per cent).

SUMMARY AND CONCLUSIONS

Forty two cases of hypernephroma were subjected to nephrectomy from 1922–1953. Twenty-two cases could be followed 5 years or more and presented a 5 year survival rate of 36.3 per cent. Fourteen cases could be followed 10 years or more and presented a survival rate of 14.2 per cent.

Including 12 cases whose surgery is less than 5 years old, it was found that of 34 cases, 18 had died in less than 5 years. These results were related to micromorphologic characteristics of the tumors, their size, and to invasion of blood vessels and perirenal tissue.

We have the impression from the literature and our cases that the greatest danger in hypernephroma is from distant metastasis. The largest problem to be solved before individual prognosis can be accurate is why tumor cells in the blood stream cause metastasis in some, but not in others.

There is a slight, but definite, indication that prognosis is worsened when renal vein, and particularly vena caval invasion exists, and when perirenal extension is present. No prognostic conclusions could be drawn in our series from the histologic appearance.

A solitary metastasis should not prevent nephrectomy if the metastasis can be removed.

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CLINICAL AND STATISTICAL SURVEY OF RENAL TUMORS ENCOUNTERED IN OUR PRACTICE

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This presentation is a study of the renal tumors encountered in the private practice of Urology in a medium sized city with no large hospital or medical center. Inasmuch as many urologists work under similar circumstances, we thought that it would be of interest to compare our findings and results with the reported series which are usually from large institutions with established services and residencies.

From 1946 to 1953, 27 cases of proven kidney tumor were encountered. We will present a statistical survey, review the literature and discuss certain of these tumors.

In the series, the tumors have been in frequency of:	*Cases*	*Cases*
1. Hypernephroma (parenchymal tumors)		17
2. Tumors of the renal pelvis		8
A. Papillary carcinoma	5	
B. Squamous cell carcinoma	2	
C. Hemangioma	1	
3. Wilms tumor		1
4. Lipoma of the kidney		1

HYPERNEPHROMA

Carcinoma of the parenchymal tissue of the kidney is by far the most common tumor of the kidney. Graham summarized 195 cases of renal tumors in 1947 and found that the vast majority encountered were those of the parenchyma. Lowsley and Kirwin have classified these tumors into 3 different groups:

1) Clear cell or Grawitz tumors, probably arising from collecting tubules of the kidney, which are usually encapsulated and fairly well circumscribed.

2) Adenocarcinoma with papillary type formation and granular type cell originating from the convoluted tubules.

3) Mixed transitional cell form containing both clear and granular cell types.

Seventeen patients had hypernephroma. Nine were in females and eight in males. The ages were between 29 years and 79 years. Two occurred between the ages of 30 to 40 years; three between the ages of 40 to 50 years; six between the ages of 50 to 60 years; five between the ages of 60 to 70 years and one between 70 to 80 years. Occupations were varied and had no statistical significance.

The first symptoms in the order of frequency follow: hematuria, 9 cases; pain in the side, 6 cases; hematuria and pain, 3 cases; weight loss, 2 cases; mass, 1 case. Other symptoms were anorexia, frequency, urgency and nocturia.

The finding of hematuria agrees with the conclusions of Lowsley and Kirwin. Although hematuria is the most frequent presenting symptom it is, most un-

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fortunately, too late as it represents invasion of the pelvis by tumor. In Graham's series, mass was the most common, occurring in 41 per cent. In this series it is less than 6 per cent.

Thirteen of the 17 cases revealed varying degrees of anemia. Papanicolaou stains were performed on 5 cases of which three were suggestive of renal tumor. Two were reported as positive, one of which was inoperable.

Perirenal air insufflation, according to the Duff method, was performed in only 1 case. This was done to determine the operability of the case. It was only proved inoperable on surgical exploration.

The workup was performed almost immediately after the patient reported. All had retrograde pyelograms. Eleven had excretory urograms. An interesting finding was that many times the calyx will not fill by gravity, but on repeating the filling with pressure a new calyx, usually elongated and compressed, may be discovered. The most common findings were compression of calyces, compression of pelvis, elongation of calyx, dilation of pelvis, calcification in tumors and obstruction to ureter, in that order. Graham, in his series, did retrograde pyelograms in 72 per cent of his cases of which 66 per cent were diagnostic. In his series, only 16 per cent of the excretory urograms were significant. There is no doubt that retrograde pyelography is the cornerstone of diagnosis. Arteriography was not used, but undoubtedly has definite diagnostic value in selected cases.

Surgical excision was performed in all cases where possible. The type of exposure varied. The translumbar route was used with resection of either the eleventh or twelfth rib in 10 cases; four through a lumbar incision alone; two transperitoneally; and one transthoracically. We were impressed that the transthoracic route added little benefit over the rib removal or Hess incision to compensate for the extra trouble and hazard.

In our series the tumor showed a distinct predilection for the right side, twelve being found on this side as compared with five on the left. Twelve of the tumors occurred in the lower pole, one in the upper pole, one in the midportion and three were generalized, and of these, two were inoperable.

There was no differentiation as to sex, nine occurring in females and eight in males.

Nine patients have expired, survival varying from 2 months to 33 months, the average time being 9 months. Practically all died of carcinomatosis. Eight are living and well. Their longevity, postoperatively, ranges from 8 months to 67 months, the average being 26 months. There does not appear to be much correlation between the size and encapsulation of the tumor and longevity. One of our patients who, at the time of surgery, revealed an extensive tumor which we felt involved the renal pedicle and vein, is still alive and well for 44 months.

A typical case history will be presented.

C. G., a 79 year old merchant, had been followed as an outpatient for 4 years and treated for a urethral stricture. Approximately 1 week prior to hospitalization on December 1, 1950, he began to have gross, painless hematuria without the passage of clots.

Neither kidney was palpable through the obese abdomen. At cystoscopy blood tinged urine appeared from the left kidney. Retrograde pyelograms revealed the right kidney and ureter to be normal. The left renal pelvis was slightly enlarged with a deformity in the outline of the lower major calyx.

Nephrectomy was performed on December 13, 1950 through a left lumbar incision with resection of the twelfth rib. A large tumor was found on the lower pole; the diagnosis was hypernephroma revealing clear cells. The perirenal fat and renal vein were found to be involved with the tumor. As much of the fat was removed as possible. Convalescence was satisfactory although 3 weeks after operation he had a superficial secondary hemorrhage from the incision and a hematoma was evacuated from the wound.

Since discharge the patient has done well except for intermittent anemia for which he receives transfusions.

MALIGNANT PAPILLARY TUMORS OF RENAL PELVIS

Tumors of the renal pelvis have been classified by Melicow into papillary including papillomas and papillary carcinoma and nonpapillary comprising a group of squamous cell carcinoma.

Papillary tumors of the renal pelvis are much more rare than those of the parenchyma and most of these are malignant. MacKenzie and Rattner stated that 5 to 7 per cent of all renal tumors are in the pelvis. These tumors may be single or numerous. Metastases are frequent in the ureter and bladder. Kimball and Ferris collected 74 cases from the literature in which they found metastases in the ureter and bladder in 50 cases. This occurred by direct extension or implantation. The papillary type is of low malignancy while the squamous cell type is highly malignant.

In our series there were 5 cases of papillary transitional cell carcinoma of the renal pelvis. The patients ranged between the ages of 57 and 82 years. There were 3 males and 2 females.

Retrograde pyelography was performed alone in 2 cases, whereas both excretory urography and retrograde pyelography were performed in 3 cases. Cystoscopy with retrograde pyelography is necessary, since metastatic lesions of the bladder frequently occur and can be missed by an excretory urogram. In papillary carcinoma of the bladder we also believe that an upper tract study is essential to rule out the frequent occurrence of involvement of the renal pelvis and ureter. A Papanicolaou stain was performed in only 1 case and this was reported as negative.

Hematuria as the presenting symptom was found in all 5 of our cases; anorexia in 4 cases.

Histologically the diagnosis was papillary transitional cell carcinoma. The lesion occurred 4 times on the right and once on the left, which is in agreement with other authors.

Nephro-ureterectomy and partial cystectomy is the procedure of choice. In our series this was done only on 1 patient; the others were not in physical condition to withstand the surgical procedure. In 2 cases a Hess activated catheter was employed. Both of these patients are alive and well, 8 months and 40 months respectively. Only one of the series has expired, and this patient died of metastases from the renal tumor and the prostate. One patient has recurrent papillary vesical tumors.

Mr. F. H., age 81, presented himself on April 4, 1951 with a chief complaint of painless hematuria of 5 weeks' duration.

Physical examination revealed mild anemia. The kidneys were not palpable or tender. The prostate was small and firm. A Papanicolaou smear was negative.

Excretory urography revealed poor function and a filling defect of the left kidney. At cystoscopy blood was noted coming from the left ureteral orifice. A filling defect of the left renal pelvis was present on retrograde pyelography.

A left lumbar nephrectomy was performed on April 20, 1951 and revealed the pelvis to be filled with a bluish-red papillary tumor. Microscopic section revealed papillary masses of transitional cells with moderate numbers of mitoses. Because of the patient's age it was decided to use a Hess activated catheter. This was employed 8 days after surgery and was left in place approximately 3 days. The patient was seen recently and is well and free from any signs of carcinoma including bladder inspection 40 months postoperatively.

SQUAMOUS CELL CARCINOMA OF THE RENAL PELVIS

This group comprises a small portion of pelvic tumors. Oberkircher, Staubitz and Blick found 121 cases reported to 1951 and stated that this type of tumor represented 17 per cent of all pelvic tumors. Probably many of these tumors are overlooked because of the relationship between the infection and calculi. Eighty-seven per cent of the patients have pyuria and 66 per cent have weight loss. Pain is the most frequent symptom. The diagnosis is often confused with pyelonephritis, renal tuberculosis, hydronephrosis and renal calculi. Metastases are frequent. The treatment of choice is early nephrectomy; x-ray therapy is of little value. The prognosis is extremely bad (Oberkircher, Staubitz and Blick).

In our series only 2 such tumors were encountered, both in females, one sixty and one 63 years of age. Retrograde pyelography was employed for diagnosis. One occurred on the right side, the other on the left.

The presenting symptom was pain in 1 and painless hematuria. Both had anemia, only 1 pyuria.

Lumbar nephrectomies were performed on both. One expired after 3 months. The other expired 10 months after surgery.

Mrs. E. V., aged 63, when admitted on October 29, 1953, complained of intermittent hematuria of 16 days' duration. She also complained of a marked frequency and urgency and a weight loss of 70 pounds in 2 months.

The kidneys were not palpable or tender. Cystoscopy disclosed hematuria from the right kidney. Retrograde pyelograms revealed an irregularity of the pelvis. The hemoglobin was 10.5 gm.; red blood cells were 3,600,000. The urine contained both red blood cells and white blood cells. Chest x-ray was negative. Nephrectomy was performed on October 30, 1953. The mucosa of the kidney pelvis was thickened. Microscopically it revealed irregular, solid masses of atypical squamous cells with frequent mitoses. Convalescence was satisfactory. This patient expired 10 months postoperatively.

PERIRENAL LIPOMA OF KIDNEY

J. D. M., aged 19, a recent bride, was unable to complete her honeymoon due to severe pain in the left lower quadrant. She had no urinary or menstrual symptoms. A large mass, both visible and palpable, was noted in the left lower abdomen. A flat film revealed an increased density, but did not definitely outline a mass. Her surgeon felt he was dealing with an ovarian cyst. At laparotomy, which was performed on July 8, 1953, it was found that the mass was retroperitoneal with a protruding lower end. It involved the whole kidney region and filled the entire vault of the diaphragm. The presence of fresh hemorrhage gave it the appearance of an embryonal growth. The kidney was fairly normal in appearance and in the center of the mass. When the pedicle was severed, removal was easy. The pathologic diagnosis was perirenal lipoma weighing 1480 gm. and as large as a football.

The right kidney, upon inspection, was normal in size but had chunks of firm fat incorporated in the capsule. This may have been an early stage of the process so far advanced on the left.

Although excretory urography is normal at present, the prognosis is guarded because of the possibility of further growth of the lipomatous process (Pfeiffer and Gandin) or sarcomatous degeneration.

HEMANGIOMA OF THE KIDNEY

This, too, is a rare lesion of the kidney; only 4 to 5 cases have been reported to 1948. Many cases go undiagnosed because the lesion is difficult to see urographically. E. T. Brill found 1 case in 30,000 autopsies; Ruby and Swanson, 1 case in 13,219.

The characteristic symptom is almost always gross hematuria associated, at times, with heavy lifting, dull ache in the flank, frequency and urgency.

It is suggested by a history of hematuria for several years without changes in the kidney.

Treatment is supportive unless bleeding is severe or the diagnosis is doubted. Then, exploration and possibly nephrectomy are indicated.

Mrs. N. S., aged 25, had onset of gross hematuria 1 day prior to admission on June 26, 1947, associated with some colicky pain on the right side. She had associated dysuria and vomited once.

Physical examination disclosed some tenderness to pressure over the right kidney, but the kidney was not palpable. The remainder of the physical examination was normal.

Urinalysis revealed 3 plus albumin with many red blood cells and white blood cells. The hemoglobin was 76 per cent and there were 3,850,000 red blood cells.

At cystoscopy, blood was seen spurting from the right orifice. A retrograde pyelogram revealed a normal ureter but angulation of the ureteropelvic junction. The pelvis was enlarged. There was widening of the calyx between the middle and lowest calyces.

On July 8, 1947 the kidney was explored through a lumbar incision. It was opened and as the tissue appeared abnormal, it was removed. The pathologic diagnosis was hemangioma of the kidney.

WILMS' TUMOR

This type of tumor is the most common type of malignancy found in children. It usually occurs in the first 3 years of life and is rare after the age of 10, although several cases have been reported in adults. It is most frequently diagnosed by the appearance of a mass in the flank; this was present in 85 per cent of cases. Treatment is early nephrectomy. Controversy still exists whether x-ray should be used pre- or postoperatively, or both. Prognosis is extremely poor with any treatment. McNeal and Chilko had a 90 per cent mortality in a series of 383 cases.

We had 1 such case which occurred in a 6 month old boy. The mother noticed a mass in the left abdomen 3 months prior to seeking help. The child looked well and was well nourished. A large mass was easily visible and palpable in the left abdomen when the child was first seen on June 10, 1953.

Intramuscular pyelography revealed a distorted pelvis and calyces. Retrograde pyelogram revealed a large renal shadow on the left with distortion of the pelvis and calyces.

A nephrectomy was performed transperitoneally on June 18, 1953 without preliminary x-ray therapy. The patient expired a few hours postoperatively.

The kidney weighed 910 gm. Microscopically the cells were very anaplastic and were in diffuse sheets, irregular cords and solid alveoli. Mitoses were moderately frequent.

SUMMARY

Twenty-seven cases of various type tumors of the kidney and pelvis have been presented together with a brief review of the literature and the presentation of illustrative cases.

CONCLUSIONS

Hypernephroma is by far the most common type of renal tumor. In our series it showed a marked predilection for the right lower pole.

Squamous cell carcinoma and Wilms' tumors appear to be the most malignant.

Early nephrectomy is the treatment of choice in all cases and nephroureterectomy in papillary transitional cell carcinomas.

Early workup with pyelography after onset of symptoms must be emphasized. Papanicolaou stain does not appear to aid appreciably in the diagnosis.

Translumbar route with removal of the eleventh or twelfth rib has been the most satisfactory method of approach.

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BILATERAL URETERAL COMPRESSION WITH OBSTRUCTION FROM A NONSPECIFIC RETROPERITONEAL INFLAMMATORY PROCESS: CASE REPORT

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Extrinsic ureteral obstruction from a retroperitoneal inflammatory process was first described by Ormond in 1948. Further case reports attest that this condition represents a urological entity; however, fundamental knowledge concerning the etiology and pathogenesis of this disease is still lacking.

Amselem, in 1950, reported an example of ureteral obstruction from this cause. In 1952, Ewell and Bruskewitz encountered a similar case. Miller et al., in 1952, added 2 patients and in the following year, Bradfield presented an instance of this process.

An eighth case is described to emphasize the difficulties which may arise in the management of ureteral obstruction from this cause.

CASE REPORT

Mrs. S. L., a 34 year old mother of 3 children, was referred to the Hartford Hospital by Dr. Robert Walker with a history of dull, persistent, progressive, left flank pain for 3 months. Three weeks before entry, she had backache, fatigue, anorexia, nausea, vomiting and vesical irritability. Her face became puffy without change in body weight. Cholecystectomy and appendectomy were done in 1943.

On examination, she was pale and showed evidence of both acute and chronic illness. The blood pressure was 160/110 mm. Well healed right abdominal scars were present. There was tenderness in the left flank and left upper abdomen.

The urine was acid with a specific gravity of 1.003. An occasional white blood cell and a rare red blood cell were noted in the sediment. Hemoglobin was 8.0 gm. with a red blood count of 4,000,000 per cubic millimeter. The white blood count was 13,400 per cubic millimeter. The nonprotein nitrogen was 90 mg. per cent. The blood uric acid was 8.1 mg. per cent. Serum calcium was 9.3 mg. per cent and the serum phosphorus was 8.8 mg. per cent. The creatinine was 7.5 mg. per cent. Serology was negative and urine cultures were sterile. The blood sedimentation rate was 96 millimeters in 1 hour. Serum proteins were 6.1 gm. with an A/G ratio of 4.1/2.0.

A chest film was negative. There was nonvisualization of the kidneys after excretory urography on May 26. Her urinary output remained satisfactory. A urological consultation was requested.

Cystoscopy (May 28) demonstrated a normal bladder. Indigo carmine appeared only from the left side. Bilateral hydronephrosis and hydro-ureter were demonstrated (fig. 1, *A*). Extrinsic ureteral obstruction of either inflammatory or neoplastic origin was suspected.

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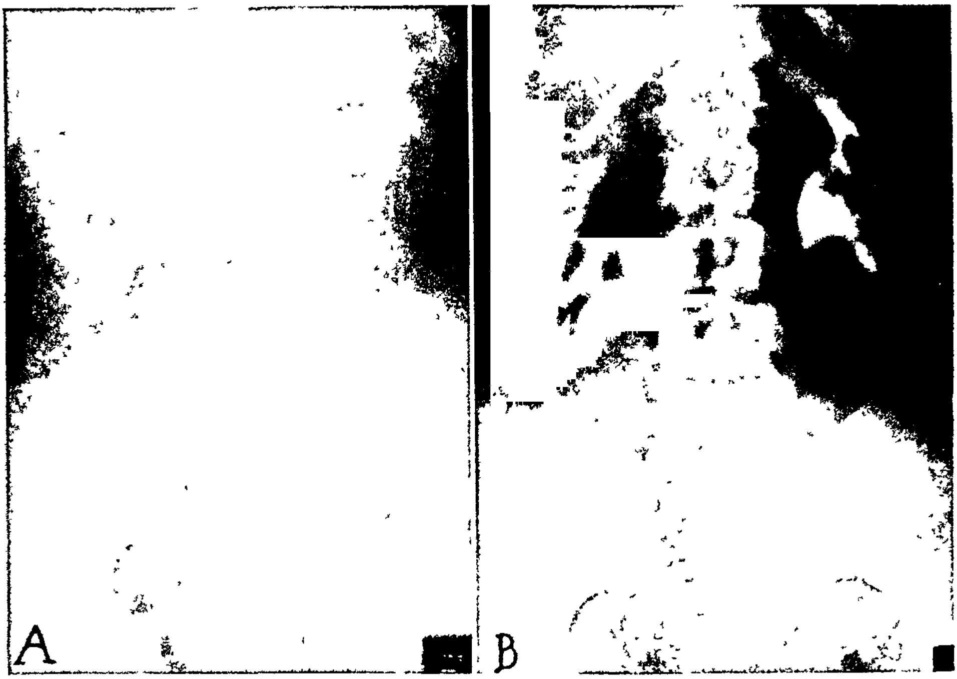

FIG. 1. *A*, bilateral pyelo-ureterogram illustrates ureteral obstruction at level of L5 from retroperitoneal inflammatory process. Right renal pelvis is incompletely filled. *B*, bilateral pyelo-ureterogram demonstrates final postoperative result and acquired diverticulum of left ureter.

The patient became anuric which necessitated ureteral catheterization on May 29. The catheters were left in place and marked diuresis resulted. Oxytetracycline was prescribed in 250 mg. doses every 6 hours. The nonprotein nitrogen was 53 mg. per cent on June 5. The ureteral catheters were changed on June 8 and pyelograms showed no significant alteration in the roentgen appearance of the kidneys or ureters. A 4 plus B. proteus infection was present.

On June 9, the left ureter was explored through a low, left flank incision. The lower pole of the left kidney was exposed and the left ureter isolated. It was encompassed and compressed by a broad band of inflammatory tissue in its middle third. The ureter was freed by sharp and blunt dissection and a biopsy of the retroperitoneal tissue was obtained (fig. 2). Ureteral drainage was maintained. Sulfamethyldiazole was administered in 0.5 gm. doses every 6 hours. The left ureteral catheter was removed on June 12 and the sutures with drain on the sixth postoperative day.

On June 16, the right ureter was explored in a similar fashion and also was surrounded by an inflammatory process. It was freed from the encompassing tissue and ureteral drainage effected with an indwelling catheter until June 19. The sutures with the drain were removed on the sixth postoperative day. She received two transfusions during her hospital stay.

At the time of discharge on June 24, the nonprotein nitrogen was 28 mg. per cent and the hematocrit 33.5 per cent. Urine culture showed a 1 plus growth of enterococci from the bladder. Excretory urography on July 20 demonstrated satisfactory function with mild bilateral hydronephrosis.

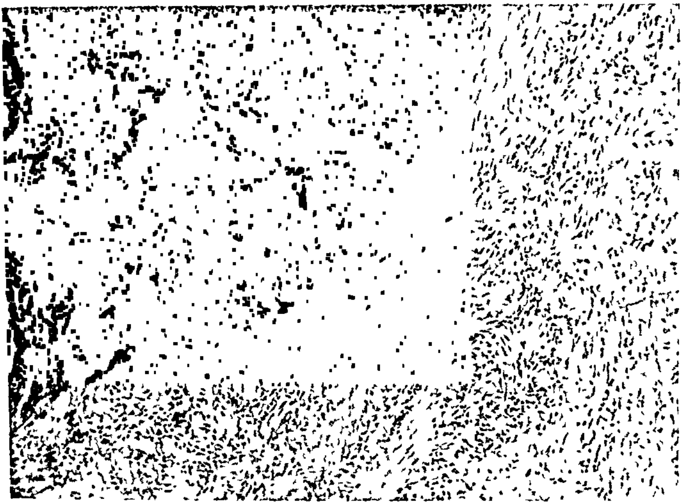

FIG. 2. High power photomicrograph showing fragment of fibrofatty tissue with chronic inflammatory reaction.

On November 5, she experienced pain in the left flank and lower back with a palpable, tender, left kidney. Excretory urography revealed mild, right hydronephrosis with nonvisualization of the left kidney. She was readmitted to the Hartford Hospital the following day.

Urinalysis showed an acid reaction with a specific gravity of 1.005. There was a 2 plus albuminuria. Occasional white blood cells and 2 plus red blood cells were seen. The hematocrit was 35.5 per cent and the white blood count 9,600 per cubic millimeter. Nonprotein nitrogen was 33 mg. per cent and urine cultures were sterile.

Cystoscopy was done on admission. No jets of urine appeared from the left orifice with some obstruction to a 5F ureteral catheter in the lower third of the left ureter. The right renal pelvis was readily catheterized. Hydronephrosis was most marked on the left with ureteral dilatation down to the upper third of the sacrum with normal caliber below this point. The catheters were left in place. She received sulfamethylthiadiazole in 0.5 gm. doses four times daily. On November 11, pyelo-ureterograms were repeated without demonstrable change. A 7F ureteral catheter was re-introduced to the left kidney and left in place.

On November 13, the left ureter was explored through a lower, left oblique gridiron incision. The ureter was markedly thickened and adherent. It could not be safely separated from the iliac artery; therefore, it was mobilized above and below this vessel and the adherent portion resected. An end-to-end anastomosis was performed with 00000 chromic catgut over the inlying catheter. Pathological examination of the removed segment of ureter showed scarring and chronic inflammatory reaction with ulceration of the mucosa.

The postoperative course was complicated by profuse urinary drainage through the wound. Injection and removal of the left ureteral catheter on November 30 showed moderate left hydronephrosis. The lower left ureter was poorly demonstrated. The abdominal sinus tract was drained with a Foley catheter. On December 6, a 4F ureteral catheter was introduced to the left kidney. Pyelograms outlined a ureterocutaneous fistula which originated at the level of the left sacro-iliac synchondrosis. Hemolytic staphylococcus was cultured from the urine. Erythromycin was given in 100 mg. doses every 6 hours. On December 14 and 21, a 8F rubber ureteral catheter was passed to the left renal pelvis and left in place. On December 22, the catheter was removed from the operative wound. The ureteral catheter was withdrawn on December 24, she remained dry and was discharged. Her hematocrit was 37 per cent. The nonprotein nitrogen was 23 mg. per cent and a urine yielded culture from the bladder B. coli.

Excretory urography on March 27, 1954 showed mild bilateral hydronephrosis. She was admitted for the third time on May 7 with a 2 weeks' history of dull, aching pain in the left flank with urinary frequency, dysuria, nausea and vomiting. Moderate left flank and upper abdominal tenderness were elicited. Urinalysis was negative except for a specific gravity of 1.002. The nonprotein nitrogen was 30 mg. per cent. The leukocyte count was 11,400 per cubic millimeter and the hematocrit 39 per cent. On May 8, cystoscopy and pyelography showed an acquired diverticulum of the left ureter (fig. 1, *B*). The colon bacillus was cultured from the left kidney and bladder. She was discharged on chloramphenicol May 14 and has remained well.

DISCUSSION

Acute and chronic inflammation of the retroperitoneal fat with fibroblastic activity and scarring may lead to bilateral extrinsic ureteral obstruction with hydronephrosis.

This disease may be unilateral initially; however, both ureters eventually become involved. Reduced health, back pain with or without colic, unexplained anemia, progressive azotemia, oliguria, and sudden total anuria seem to be the dominant clinical features.

All causes of renal insufficiency may require consideration, but cystoscopy and retrograde pyelography are mandatory for diagnosis. Extrinsic ureteral compression without stricture will be found. The differential diagnosis revolves about either a neoplastic or an inflammatory process. The diseases to be excluded are: malignant lymphoma; reticulum cell sarcoma; Hodgkin's disease; metastatic invasion and peri-ureteritis plastica. Similar but reversible ureteral changes which may lead to confusion have been noted in such diverse and unrelated inflammatory processes as regional ileitis, acute cholecystitis, orchitis, appendicitis, parametritis, and oöphoritis.

The treatment has not been standardized. Bilateral nephrostomy with secondary ureterolysis by both the intra- and extraperitoneal approaches have been done. Nephrectomy with nephrostomy and intra-abdominal ureterolysis on the opposite side have been performed. Renal exploration followed by antibiotic therapy with Q 19 has been utilized Deep x-ray therapy after surgery was tried in one case

More experience will be required before a definite plan of therapy can be formulated In the case under consideration, drainage was maintained with indwelling ureteral catheters and ureterolysis was accomplished by the retroperitoneal approach The postoperative result was complicated by an acquired diverticulum of the left lower ureter

SUMMARY

The eighth case of bilateral ureteral compression with obstruction from a retroperitoneal inflammatory process of unknown etiology has been presented The literature has been reviewed and the diagnosis discussed Bilateral extraperitoneal ureterolysis produced a functional result

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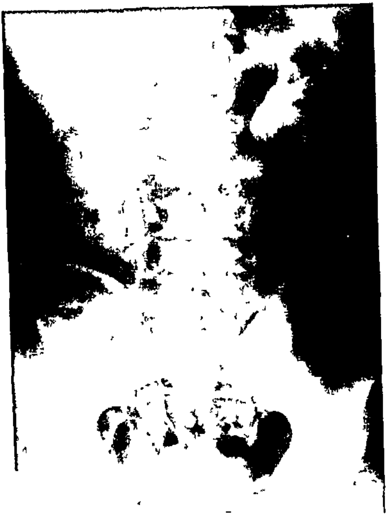

FIG. 2 Excretory urogram 4 days postoperatively following bilateral ureterosigmoidal anastomosis. Note absence of hydronephrosis in splinted side.

Figure 2 is an excretory urogram 4 days postoperatively, in which the splinting catheter was used only on the right side for a comparison. The pyelogram shows hydronephrosis on the side of the implant where no splinting catheter was used, and an empty kidney on the side of the splinting catheter, indicating the prevention of an immediate postoperative hydronephrosis by the use of a splinting catheter.

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SURGICAL REPAIR OF THE LOWER URETERS AND BLADDER WHICH HAVE BEEN INJURED DURING PELVIC SURGERY

MILTON M. COPLAN, FRANK M. WOODS AND PERRY D. MELVIN

The purpose of this paper is to present a concise description of operative technique for repair of the lower ureters and bladder, injured during pelvic surgery, that has been found successful in our private practice. No attempt is made to describe the various causes, types of injuries, statistics, or the multiple operative procedures undertaken to achieve the same end. A more extensive discussion of the subject was presented by us at the Southeastern Section of the American Urological Association at its annual meeting at West Palm Beach in 1954, in which we quoted from Drs. Leon Herman, David Feiner, R. J. Prentiss, R. B. Mullinex, Charles Higgins, Paul W. Aschner, T. D. Moore, Eugene St. Martin and others who have discussed many aspects of this condition. This paper has been published in the 1954 Transactions of the Southeastern Section.

Lower ureteral injuries are becoming more common with the advent of radical pelvic surgery. It is the duty of the urologist to co-operate in every way possible to prevent, as well as to correct, these injuries.

One of the easiest and surest methods to prevent injury to lower ureters and bladder during pelvic and lower colon surgery is placing large, indwelling ureteral catheters in the ureters, and a Foley type catheter in the bladder preoperatively. These can be tied together just outside the urethral meatus with a small piece of umbilical tape to prevent slipping during the transfer of the patient from the cystoscopy table to the operating table. This procedure is an aid to prevent injury, but must not give the surgeon a false sense of security nor encourage him to fail to use extreme care at all times to preserve continuity of the urinary tract.

The most opportune time to repair an injured ureter is at the time of injury if it is recognized and is not too extensive. Simple incision into a ureter should be closed with absorbable suture, chromic 00 to 0000, and drained extraperitoneally. Teaming with a cystoscopist is frequently desirable for more extensive ureteral injuries during the primary operation. The distal segment of a cut ureter is frequently clamped and ligated with the uterine artery and is difficult to expose. Without moving the patient from the table, her legs are spread and lifted under the sterile drape sheet by an attendant. The foot of the table is then dropped to a position perpendicular to the floor and two Mayo instrument stands, each padded with a pillow, are brought up under the drape so that each outstretched leg can come to rest on one. The cystoscopist sits at the foot of the table under the sterile drape sheets where he contributes his skill in passing a large ureteral catheter, bougie or a diverticulite up to the point of obstruction of the ureter. A light in the distal segment of the cut ureter makes it easy to identify when the overhead lights are turned off. We feel that end-to-end anastomosis can be accomplished in most cases and is the most satisfactory procedure. The anastomosis can be performed over a T-tube or over an indwelling catheter to preserve continuity of the lumen of the ureter. It is our practice to trim the cut ends of the ureter obliquely so that we do not have a transverse scar, and the likelihood of subsequent stricture is greatly diminished. In using the T-tube, which can be done with or without the aid of a cystoscopist, after the distal segment of the ureter is isolated, an incision is made in the ureter *above* the site of the injury and the T-tube is inserted so that one arm of the tube goes toward the pelvis of the kidney and the other down into the bladder or on out the urethra to drain the kidney and act as a splint for the injured ureter. Closure of the anastomosis is then done with an atraumatic chromic 00 to 0000. The right angle of the T-tube is then brought out extraperitoneally and the area of the wound is drained. It is frequently necessary to cut a wedge from the T-tube on the superior surface of the junction of the horizontal-vertical arms in order to remove a small plug of rubber that impairs drainage at this point (fig. 1). Removal of this wedge also reduces the possibility of trauma to the ureter when the tube is withdrawn. The T-tube is used in preference to single or multiple ureteral catheters because it usually provides for better drainage and certainly permits much earlier ambulation of the patient. It has been our policy to leave the tube in place 10 to 30 days, depending upon the severity of the injury.

Extensive and time-consuming repairs of injuries discovered during the course of the primary operation are usually impractical and require urologic surgery at a later date. If impossible to do an end-to-end anastomosis, it may be desirable to ligate the proximal ureter and insert a tube into it for drainage. This can be brought out extraperitoneally until such time as permanent repair can be done. A ureteroneocystostomy may be done rapidly in some instances where end-to-

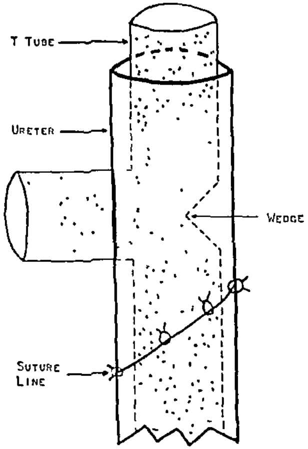

FIG. 1

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DIGITAL EXTRACTION OF BLADDER CALCULI IN A FEMALE PARAPLEGIC

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A 21 year old white woman was brought to the emergency room of St. Luke's Hospital because of caking and poor drainage of her indwelling Foley catheter. Four years previously she had been in an automobile accident at which time she sustained an injury to the spinal cord resulting in paralysis of both lower extremities as well as the bladder and bowel. After a spine fusion operation in the area of D11, she attended a rehabilitation center in Boston for 10 months, but showed no progress and finally returned home. She remained in bed, during which time her bladder dysfunction was managed by an indwelling catheter with daily irrigations of 1–20,000 aqueous zephiran solution. The catheter was changed about once a month. She took various types of urinary antiseptics on occasion, when the urine seemed particularly purulent.

A few days before she appeared at the emergency room it was noticed that the catheter would not drain well spontaneously, nor could it be irrigated effectively. It was thought by her family physician that she probably had the usual alkaline encrusted cystitis so common with long-standing indwelling catheter drainage, and that some of these crusts had partially blocked the tube. He advised urological consultation.

The 21F Brown-Buerger cystoscope was introduced into the bladder, immediately producing a grating sensation and sound characteristic of rubbing metal on stone. It was possible to distend the bladder sufficiently with fluid so that observation to a certain degree could be carried out, which confirmed the presence of numerous calculi in the bladder. A plain film of the abdomen was taken to determine further the extent of the calculous deposits in the bladder and to ascertain the size of those stones which could not be visualized cystoscopically, as well as to rule out the presence of lithiasis in the upper urinary tract (fig. 1, *A*).

While the film was being developed, we contemplated with great concern the thought of having to operate upon a young woman who had already had more than her share of tragic experiences. At this point, it occurred to us that perhaps in a female paraplegic patient with a short urethra, and with patulousness and atony of the sphincter and bladder neck, a finger might be inserted into the bladder and the stones removed by digital manipulation. It was felt that certainly many of the smaller ones could be extracted this way; the fate of the larger ones could not be told until the procedure was tried.

Having determined that the urolithiasis was confined to the bladder, and having an idea of the extent of the calculous deposits, the fifth finger was in-

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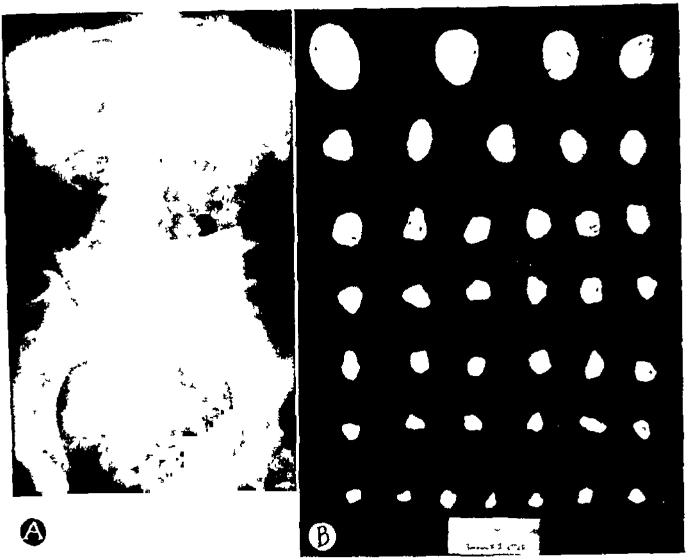

FIG 1. *A*, x-ray prior to manipulation. *B*, stones removed digitally.

serted transurethrally into the bladder. Of course no anesthesia was required in view of the paraplegia. Discovering that the urethra admitted the fifth finger readily, this finger was removed and in its place the index finger was inserted. The smaller calculi were brought down between the ball of the index finger and the urethral wall and gently teased all the way out. There remained 5 larger ones which would warrant suprapubic cystolithotomy in the ordinary case. (We have ordinarily been loathe to carry out litholapaxy or lithotriptoscopy because in our experience the small fragments of stone are frequently ground into the lining of the bladder and act as a nidus for subsequent infection and further stone formation.) It seemed perfectly reasonable therefore to continue this same technique in attempting to remove the larger stones. It was striking how readily the index finger of the right hand could bring the almond-shaped stones into the posterior urethra. At this location the stone was engaged by using two fingers of the left hand to press upward on the anterior vaginal wall, thus preventing the stone from slipping back into the bladder from the posterior urethra. The fingers of the left hand in the vagina were pressed against the proximal end of the long stone in the urethra, and thus made the distal end present visibly at the external urethral meatus. Then the thumb and index finger of the right hand gently rotated the stone on its long axis until it was delivered. This procedure was repeated until no further calculi could be felt in the bladder. The cystoscope was reinserted, and the absence of residual calcific

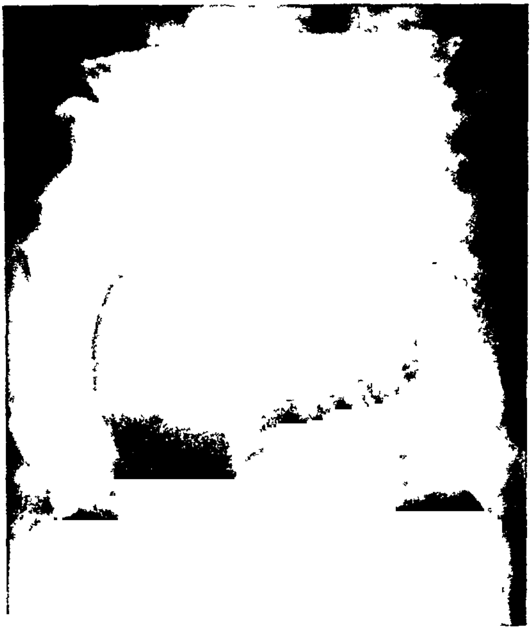

FIG. 2. X-ray following manipulation.

deposits was confirmed. It was striking how relatively healthy the bladder mucosa appeared after this procedure. There was no evidence of trauma.

Forty stones in all were removed (fig. 1, *B*). These ranged all the way from 4 cm. in the largest diameter to several that were only 7 mm. Many had the three-dimensional shape of a date and others had the more typical flat or plaque-like shape that is commonly encountered in this type of problem. They all presented an off-white color. Chemical analysis subsequently revealed them to be composed of phosphate with a trace of calcium carbonate. The urinary pH was 8.0. There were numerous pus cells in the sediment. The culture revealed a mixed infection of E. coli and nonhemolytic staphylococci and streptococci. Sensitivity tests revealed these organisms to be responsive chiefly to furadantin.

The entire manipulation took less than 10 minutes following which a plain film of the abdomen showed no stones at all present (fig. 2). The appropriate follow-up therapy was prescribed, and the patient was back in her home less than an hour from the time she was first seen in the emergency room.

COMMENT

The concept of removing vesical foreign bodies through the urethra in a female was discussed by McCune in 1952. He mentioned in particular thermometers and eye droppers and wished to avoid breaking them with mechanical instruments, His cases were in relatively normal females, i.e., without paraplegia. Frankly, when we first noted this article we were not favorably impressed, since we felt that the procedure was not particularly physiological, and we were concerned about the outcome of the sphincter's integrity after such a seemingly traumatic experience. Although Dr. McCune's results tended to justify his procedure, we were unable conscientiously to accept it as good surgical technique and promptly discarded the thought. However, when faced with our situation, and the thought suggested by this report 2 years previously flashed through our minds, it seemed like a reasonable thing to try. The results were gratifying.

It would seem that *many paraplegic women with this all-too-frequent complication in the urinary tract might well be saved an open surgical procedure* by considering this simple method of digital extraction that can actually be done in the office or at home. We should like to commend it to your attention and will be pleased to have your comments at a subsequent date regarding your own experience with it.

SUMMARY

A case of a young woman with multiple bladder stones complicating paraplegia has been presented. Open operation was avoided by the simple measure of removing the stones by digital manipulation through the urethra.

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THE USE OF A FREE CUTIS GRAFT IN THE OPERATION FOR URINARY STRESS INCONTINENCE

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Stress incontinence due to laceration of the urethral sphincter is evident by small evacuations of urine when the patient coughs, sneezes, strains, steps off a curbing, etc. This condition may progress to total incontinence.

The statistics[1-6] of operative failures range upwards from 10 per cent. This indicates that there is considerable room for improvement in our knowledge of the underlying causes leading to stress incontinence and the proper techniques for cure.

The anatomy of the urethra and adjacent tissues has been well presented by recent investigators.[6-9] Our knowledge of the physiology of the urethra is still a subject for further clarification. Our knowledge of the tissue change is based largely upon clinical observations which are limited to the posterior (vaginal) aspect. Interesting roentgen studies have been made.[10-12] No report of a study was found that investigated the possibility of injury to the anterior (pubic) aspect of the urethra.

In 1914, Kelly advocated the restoration of the sphincter by imbrication during which he used a single mattress suture near the bladder junction. Since this method was modified to include most of the urethra, many modern techniques have used this method as a basic maneuver. When it was found that the modified Kelly operation still permitted 20 per cent or more failures, additional procedures were introduced. At present some authors[1, 3, 5, 12, 13, others] attribute the cause of these failures to a displacement of the urethra which interferes with a lever action employed by the sphincter muscle. Several methods which employ a

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TABLE 1 *Results following operation (no failures)*

Case Number	Previous Operations for Incontinence	Age Insertion of Graft	Complete Control	Follow Up
1	2 (also prolapse)	64	immediately	6 yrs
2	1	35	immediately	6 yrs
3	1	50	immediately	4 yrs
4		75	immediately	4 yrs
5		37	immediately	4 yrs
6	1	45	immediately	4 yrs
7		42	1 yr	3½ yrs
8		44	immediately	3 yrs
9		51	immediately	3 yrs
10		49	immediately	3 yrs
11		50	immediately	2 yrs
12		57	4 mos	2 yrs
13		52	4 mos	2 yrs
14		34	immediately	1 yr
15		39	immediately	7 mos
16		47	immediately	4 mos
17		50	1 mo	4 mos
18		49	immediately	2 mos

sling of tissue to hold the urethra "in position" have been advanced [1, 2, 4, 6]. On the other hand several authors[10, 13, 14] have approached the problem from the standpoint that the tissue layers were so inadequate that they broke down under the stress and strain of function. Shaw[14] supported these tissues by inserting a patch of fascia lata over the primary repair. Kegel[12] has shown that the atrophic tissues will respond to exercise where the extent of trauma was not too great.

Our clinical experience with the tissue planes of the urethra, perineum, vagina and upper pelvic diaphragm led to appraisals of tissue substance and strength. We observed that these tissue planes were poorly developed in many instances and appeared to be incapable of continued support. In our failures following conventional repairs in both stress incontinence and pelvic prolapse,[15] the tissue dissections at subsequent operation bore out this contention and confirmed the observations of Kegel, Shaw, and Jeffcoate and Roberts. We observed at least three conditions other than trauma which reduced tissue strength. 1) The tissues varied in degree of native development[8, 14, 15] from a strong supportive structure to one of poor substance. The former appeared to be better suited to withstand the injuries of pregnancy. Common examples of extreme lack of development of supporting structures were observed in uterine prolapse and rectocele in the nullipara. 2) Atrophy due to senile changes progressively weakened the tissue layers to a point that simple repair would not allow a permanent cure. The advancing nature of this change was often indicated in the clinical history. 3) Atrophy and subsequent loss of function through inactivity, due frequently to trauma, were noted in some degree in most cases. Atrophy of disuse has been a constant problem for the traumatic surgeon. Kegel has adapted this knowledge to rehabilitate the urethral muscle through exercise.[8, 12] It is interesting that in order to achieve success through exercise concomitant local development of the muscle and the re-establishment of the reflex of central nervous system origin must be accomplished. In case 7 the patient gained complete control through exercise after 1 year and illustrated the presence of tissue atrophy and lack of central control. Surgical repair had resulted in complete control except when she had had too many cocktails. Continued exercises finally resulted in establishing the proper reflex. In case 12 a similar condition was encountered. The "mental block" which prevented the establishment of the central reflex disappeared when her soldier son was relieved of active duty in the Korean War.

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COMMENT

It was my belief that all of the aforementioned factors were concerned in a varying degree in every case of stress incontinence due to local pathological processes. Because there was no yardstick which accurately measured these factors, I believed that this area should be reinforced with tissue grafts in every case. Perhaps this approach to the problem was too simple in conception but it has resulted in complete control of function in all of our cases.

The technique involved four major maneuvers.

1) Extensive exposure of the urethra must be done, as advocated by others.[2, 3, 4, 6] The entire length of the urethra was exposed from the trigone of the bladder to the external meatus and laterally to the pubic rami on either side. This was facilitated by freeing the bladder entirely from the uterus.

2) The urethra was imbricated in its entire length from trigone to meatus. A sufficient number of *rows* of sutures were placed to reduce the caliber of the urethra as much as possible. No indwelling catheter was used during this procedure. This appeared to be necessary because one could not outline the sphincter remnants accurately. Fine, nonabsorbable sutures were used routinely.

3) A free graft of sufficient size to cover the area exposed above in paragraph 1 was obtained from one edge of the incision in the vaginal wall and fixed in place with nonabsorbable sutures. The mucosa was closed over the graft with catgut, a small Foley catheter was inserted; and a pack was placed in the vagina for compression of the operative site.

4) When the operative site had healed and the local edema had disappeared, the patient was instructed in the exercises described by Kegel.

The results obtained in this small series are presented in table 1.

CONCLUSIONS

Our technical approach to the problem of stress incontinence has been twofold: 1) A laceration of the sphincter muscle must be repaired. 2) A loss of strength of tissue layers due to lack of native development, senile atrophy and the atrophy of disuse must be reinforced.

A free tissue graft was taken from the edge of the vaginal incision and attached to the operative area.

Perineal calisthenics repaired the functional pathological process and aided in obtaining full results.

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URETERO-ARTERIAL FISTULA

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Uretero-arterial communication can be conceived only as the result of severe inflammatory trauma at the site of the ureteral crossing by a large vessel. Ureteral juxtaposition to the large arteries of the pelvis is receiving more attention since involvement of the ureter is being observed more frequently in extensive pelvic surgery. In nearly all cases heretofore recorded of uretero-arterial fistula, an indwelling ureteral catheter has been antecedent.

Davidson and Smith reported a case in which after indwelling ureteral catheter drainage of a greatly dilated ureter in pregnancy, after a sharp, appendiceal-like pain, profound shock and hemorrhage from the bladder resulted in death. Postmortem examination showed the right ureter adherent with a communication 3 cm. long to the right iliac artery.

In all previously reported cases, the cause has been looseness of tissue construction in gravidity and pressure fracture of a large blood vessel. In seven of the 8 known cases of uretero-arterial fistula, of which only 4 cases have been recorded in detail, hemmorrhage was the cause of death. The only case with recovery was the first case reported by Moschowitz in which he performed a simultaneous bilateral iliac artery ligation.

In the following case report the instigating factors were peri-ureteral inflammation over an impacted mural calculus (fig. 1, *A*) which had been treated unsuccessfully over a 2-year period by extractors, dilators and electrothermal transurethral ureteromeatotomy, and a low retrovesical ureterolithotomy in a dilated ureter.

CASE REPORT

Florence Crittenton Hospital No. 52088-C, S. C., a 44-year old man, entered the hospital October 13, 1953. Excretory urography had demonstrated a large calculus in the lower left ureter and second degree left hydronephrosis. The x-ray report indicated that the calculus and the hydronephrotic sac were increasing in size when compared with previous films.

Through a Gibson incision, a left ureterolithotomy was performed under spinal anesthesia. By probing, the calculus was located in a densely infiltrated and edematous peri-ureteral area. The stone was removed through an incision made directly through the peri-ureteral infiltration. (In retrospect, there is the possibility that the stone had been partially extruded extra-ureterally by the previous electrothermal ureteral meatotomy.) A drain was brought out through a counter-flank puncture. The preoperatively placed left ureteral catheter was taped indwelling.

The postoperative period was badly complicated by abdominal distention and by a profusely draining, persistent urinary sinus through the angle of the incision. To control this, it was decided to perform cystoscopy 16 days postoperatively. Cystoscopy showed a large, granulomatous excrescence prolapsing from the left ureteral orifice and it was deemed unsafe to attempt catheterization.

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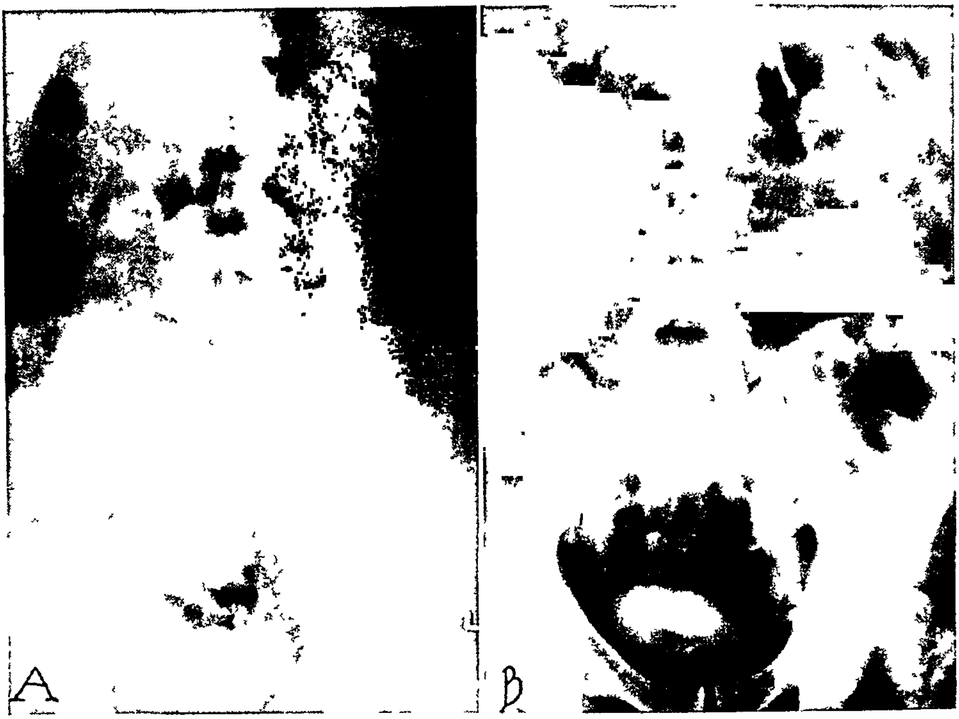

FIG. 1. *A*, calculus in left lower ureter after attempts at removal by instruments and meatotomy. *B*, excretory urogram after ureterolithotomy.

Excretory urography (fig. 1, *B*) showed normal function and pattern of both kidneys. Contrast medium from the left ureter did not enter the bladder, but was either retained in a large dilated ureter or in a pouch from extravasation into soft tissues.

Following discharge from the hospital, the patient reported gradual diminution in the amount of urinary sinus drainage. One month postoperatively he was seen in the office. The sinus had nearly healed.

Several days later I was called to his home because of sharp, tearing pain following exercises he had taken by flexing his thigh upon the abdomen, putting strain on the psoas muscle. Morphine was required for pain and the next day severe hematuria made hospital readmission urgent.

Consultation (Dr. R. P. Lytle): "Late secondary hemorrhage following ureterolithotomy. Severity of bleeding suggests invasion of a major vessel such as the hypogastric. I would not recommend extraperitoneal approach save for packing, as the vessel leak may easily be enlarged. Recommend transperitoneal approach so the iliac vessel can be immediately controlled, then probably ligation can be done."

Operation: Ligation of left hypogastric artery. Under general anesthesia a retroperitoneal approach showed no retroperitoneal blood or extravasation until retraction of the peritoneum medially resulted in arterial hemorrhage drenching the area. Digital compression of the aorta, retroperitoneally, was remarkably effective resulting in a fairly dry field. The hypogastric artery showed a long lateral tear from adhesions to the site of the ureterolithotomy incision near the mural portion. Clamping and ligation of the pulsating stump of the hypogastric artery above, and two distal stumps were easily effected.

The patient tolerated the procedure well and the operative blood loss was less than 500 cc. Although the left femoral and popliteal arteries could not be palpated the interference was attributed to the packing, which was removed in 24 hours with fair arterial pulsations. Daily blood studies showed a red blood cell count of 4.3 million that fell to 2.2 million/cu.mm. Hemoglobin and hematocrit levels were commensurate. Marked leukocytosis, with marked shift to the left, was present at all times. The white blood cell count varied from 47,400 to 20,300 per cu.mm. This was classified as a leukemoid reaction. Platelets were adequate, numbering 246,000 on one occasion. There was no depression of prothrombin. The blood nonprotein nitrogen rose from 49 on admission to 69 mg./100 ml. on the day of operation. The uncorrected sedimentation rate on the day of operation was elevated to 58 mm. in 1 hour. Blood cultures on two occasions were negative. (Dr. Edw. Zawadski.)

SUMMARY

A case of uretero-arterial fistula, due to perforation of the ureter into the hypogastric artery, is reported.

The communication was at the site of a retrovesical incision into a peri-ureteral infiltrated area and resulted from many ureteral dilatations, extraction attempts, and an electrothermal transurethral ureterotomy.

The perforation occurred 45 days postoperatively following exercises flexing the thigh and stress on the psoas muscle. Acute tearing pain with severe hemorrhage from the bladder was accompanied by a leukemoid blood reaction. Blood cultures were negative.

Progressive paralytic ileus that caused death 5 days after a successful hypogastric arterial ligation must be attributed to leukemoid reaction; because of complete insertion of the long intestinal tube and failure of electrolyte and fluid balance.

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PRIMARY AMYLOIDOSIS OF THE BLADDER

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The problem of differentiating benign from malignant lesions is particularly difficult in amyloid tumor of the urinary bladder. These tumors, though extremely rare, are easily confused with carcinoma since they have the hallmarks of malignancy: painless hematuria and the cystoscopic picture of infiltrating cancer.

We have recently treated a patient in whom localized amyloidosis of the urinary bladder developed during a year of careful observation.

CASE REPORT

I. T., a 54-year-old white, American, married woman, was seen first in the outpatient clinic in October 1952, with the complaint of intermittent, painless hematuria for the preceding 7 months. The bleeding had become profuse during the week prior to her initial visit.

Positive findings on physical examination were moderate hypertension and obesity. The urine contained gross blood, many pus cells and a few diplococci. Cystoscopic examination showed hyperemia in the mid-trigone. No other changes were noted. Excretory urograms showed normal kidneys, ureters and bladder. The hematuria subsided following treatment by aureomycin and the patient had no further complaints until 6 months later when she again had painless hematuria. The urine was found to have many red cells, a few pus cells and no bacteria on microscopic examination. Cystoscopy again showed no additional findings. During the following weeks retrograde study was done and x-rays, Papanicolaou smears, and cultures were negative. A month later, on cystoscopic examination, an erythematous area was first noted on the posterior wall of the bladder. The endoscopist felt that this finding was compatible with chronic cystitis.

The patient had no symptoms until 4 months later when she returned with the complaint of terminal hematuria. Cystoscopy showed only injection of the trigone. She was treated by antibiotics and urethral dilatations, and again the bleeding ceased until 2 months later when the fourth episode of hematuria occurred. At this time cystoscopy showed a hemorrhagic area on the posterior wall near the dome of the bladder. There were many coarse folds about this area which were raised in respect to the surrounding bladder mucosa. As the bladder distended many of these folds were diminished in the degree of their intravesical protrusion.

A clinical diagnosis of infiltrating tumor of the bladder was made. Because of the anatomical situation of the lesion a segmental resection was performed on December 27, 1953, one year and 2 months after the patient's initial complaint of hematuria.

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At the time of operation frozen section was done on the easily resected tumor. The pathologist reported that the lesion was not malignant, but suggested a curious inflammatory condition. The tumor itself was 8 cm. in diameter and measured 1 cm. in thickness. Thickening of the mucosa and submucosa was evident on sectioning the operative specimen and measurement showed the mucosal layer to be 2 mm. to 3 mm. in thickness. Grossly, the lesion resembled hypertrophic gastric mucosa. It was not until the permanent sections were made that the diagnosis of amyloid tumor of the bladder was apparent. See figures 1, 2, 3.

Following operation, search was made for other sources of amyloid disease. Laryngoscopy was negative for any nodules. The congo red test was negative—only 18 per cent absorption of the dye by the tissues. A liver biopsy with a Silver-

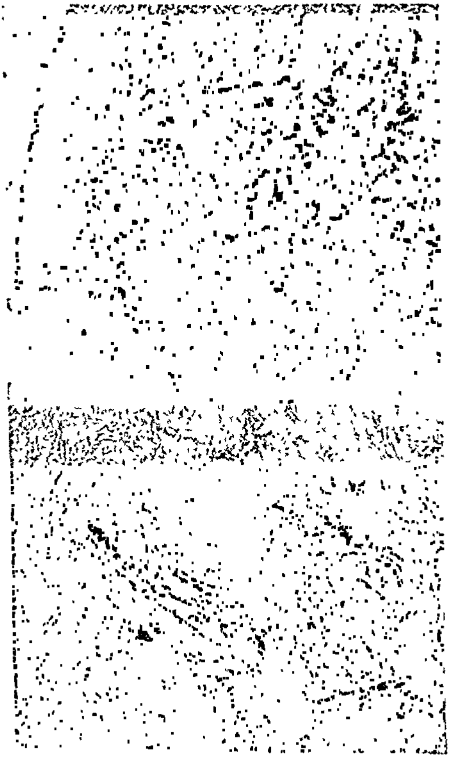

FIG. 1. *A*, section adjacent to mucosa showing thickening of mucosal layer with destruction of lamina propria and muscularis by infiltration of amyloid. *B*, large, dilated vessels in detrusor muscle surrounded by amyloid infiltration with only a few muscle fibrils remaining.

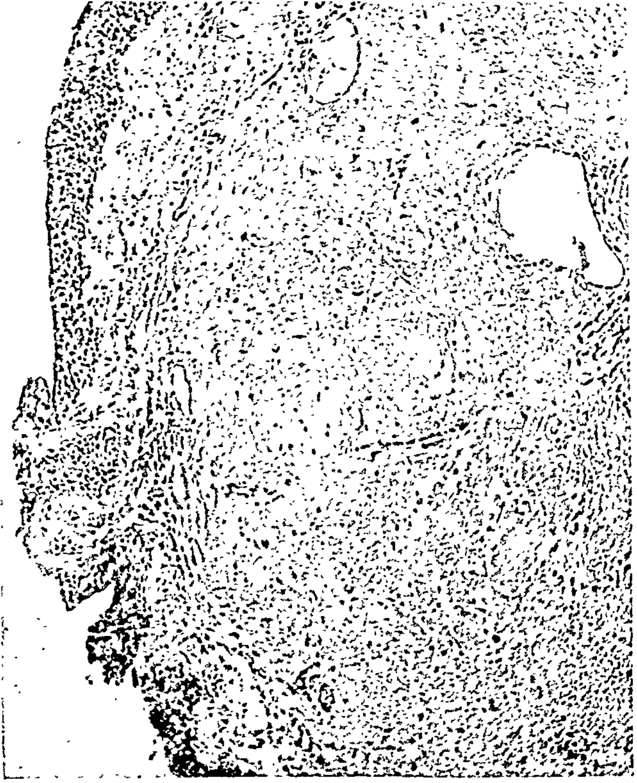

FIG. 2. Extension of amyloid deposit through mucosa leaving eroded surface seen cystoscopically as ulceration.

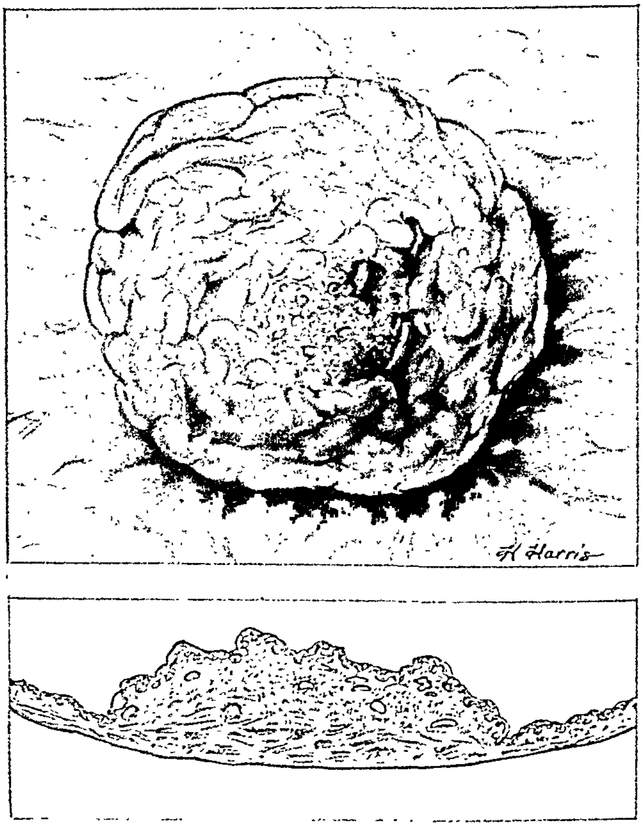

FIG. 3. Artist's drawing of gross lesion demonstrating central ulceration and rugae-like folds.

man needle showed normal liver tissue. Electrocardiogram, basal metabolism rate, blood and urine examinations were within normal limits.

Since operation the patient has done well and has had no symptoms other than urinary frequency related to decreased bladder capacity.

Examination indicates that other evidence of amyloid disease has been excluded in this case, and that this patient presents primary amyloid tumor of the bladder.

DISCUSSION

In the past 57 years 11 cases of amyloid tumor of the urinary bladder have been reported in Europe and the United States. The first case was reported by Solomin in 1897, and the second and third by Lucksh in 1904, and Chwalla in 1932—all in Europe. In the United States 8 cases have been reported; the first two by Rusche in 1941, followed by Corbett 1944, Craig 1949, Singer 1950, Roen 1951, and Poutasse 1952. The disease is not peculiar to one sex, but all cases have been more than 40 years of age.

Perhaps because of its rarity, a clinical impression of amyloid tumor of the bladder has never been made. The occurrence is so infrequent that the chances are very much against one seeing this cystoscopic picture more than once in a lifetime. All cases had the initial symptom of painless hematuria as the presenting complaint. Cystoscopic examination in all cases showed a lesion of an "infiltrating type" and all, save one thought to be papilloma, were observed as infiltrating lesions. The erroneous clinical diagnosis in all cases was invariably carcinoma of the bladder.

In only 2 cases was the lesion diagnosed by transurethral biopsy. All cases except two were treated by open operation. In those patients where the lesion was so located as to permit segmental resection it was deemed the procedure of choice. In lesions situated in the region of the vesical neck and trigone, transurethral resection has been successfully carried out and the patients have remained asymptomatic. One must be aware of the fact that in all these patients the surgeon was clinically convinced that he was dealing with malignancy and therefore proceeded in a manner which would evaluate the potentialities of this tumor.

Anderson describes four categories of amyloid disease:

1) *Primary.* A relatively uncommon condition wherein for no apparent cause, amyloid is deposited in tissues of mesenchymal origin.

2) *Secondary.* The most common variety found to occur following long standing chronic illness (tuberculosis, osteomyelitis, etc.). Here the amyloid deposits are usually found in parenchymatous organs in distinction to primary amyloidosis where the mesodermal tissues are involved.

3) *Localized amyloidosis.* This is found usually in the eyelids, larynx, bladder and skin. No amyloid tumors have been reported in the gastro-intestinal tract without coexistence of the generalized disease.

4) *Amyloidosis in association with multiple myeloma.* In this group multiple myeloma is the predominate lesion although the distribution of amyloid is similar to that in the primary disease.

Of what amyloid itself is composed remains to the greater part a mystery.

Extensive chemical analysis has revealed that amyloid is a complex protein which can be fractionated into two other proteins by organic chemical methods. These two fractions depend on a third factor, known to be a complex polysaccharide, to unite them in a compound which has the chemical and physical properties of amyloid. The staining properties with congo red and iodine are well known, and the former is used as a diagnostic test for the generalized disease. This diagnostic adjunct was described in 1923 by Bennhold and, although not infallible, it lends itself to the determination of widespread amyloidosis.

The microscopic pathology of this disease as seen in the bladder is characterized by an infiltration of the proteinaceous material within the mucosa, spreading downward to the submucosa and to a lesser extent the muscularis.

On section it is evident that a large amount of amyloid has been deposited in the extracellular spaces within the mucosa. This material accounts for the folds observed on the tumor surface during cystoscopic examination. The continuous accumulation of amyloid causes increased thickness of the mucosal layer without gross change in the muscularis in some areas. It is well demonstrated by the photomicrograph that much of the muscle has been invaded and destroyed by amyloid material which, in some areas, has completely replaced the musculature. Some inflammatory reaction of mild degree is present in the necrotic area on the surface which was the source of the hematuria.

From the localized occurrence of the tumor, it would follow that complete surgical ablation is the most effective means of cure. When feasible, segmental resection is the procedure of choice. The microscopic examination of the wall of the bladder reveals that in the area of the tumor, the muscle itself is deeply infiltrated with amyloid. It would seem that transurethral resection of the tumor would be dangerous because of altered bladder musculature and carries with it the very excellent chance that the lesion could not be entirely eradicated. Tissue death from high frequency current, on which we depend to kill tumor cells, does not in a like manner eliminate a relatively inert protein. Although the cases treated with transurethral resection have remained asymptomatic, one wonders if this is a temporary situation, and if the disease still progresses slowly in areas not completely evacuated of tumor by the transurethral instrument. The importance of removing the entire lesions lies in the possible occurrence of obstructive disease to the upper urinary tract, anemia from chronic blood loss, and pathologic rupture of the bladder.

Localized amyloid tumor remains a medical curiosity and is of importance chiefly because of its confusion with malignant disease. The keen discernment of the clinician is required to detect the true nature of the lesion. Treatment should be directed in such a manner so as to extirpate the lesion entirely. Experience has shown that this disease has not been fatal.

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SQUAMOUS EPITHELIUM IN THE TRIGONE OF THE HUMAN FEMALE URINARY BLADDER

WITH A NOTE ON CYSTOSCOPIC OBSERVATIONS DURING ESTROGEN THERAPY

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For many years, observers[1, 2, 3, 4, 5, 6, 7, 8, 9, 10] have recognized the occurrence on the trigone of the human female bladder of grayish-white patches which have been described as chronic trigonitis, pseudomembranous trigonitis, trigonitis areata alba, etc. Cifuentes[11, 12] clarified the nature of these patches; he noted that histologically they were composed of squamous epithelium and stated that they occurred exclusively in the trigonal mucosa of females. He stressed the resemblance to vaginal mucosa.

The patches under consideration occur on the trigone of females most frequently during their active sex life; their frequency appears to diminish with age, but we have observed them in the sixth, seventh and eighth decades. Such areas have never been reported in prepubertal females or in infants; however, one of us (J. C. E.) observed one such area in serial sections of the trigone of a newborn female infant.

Grayish-white patches similar to those which occur in the female have rarely been described in males. Cifuentes[12] had never seen one in a male, and Heymann[13] reported their absence in five men studied. It should be emphasized that we are not concerned here with squamous metaplasia due to calculi, tumors, ulcers and trauma. In a routine study of five hundred consecutive autopsies of both sexes and all age groups, the present authors have not observed squamous patches of this type in a single male.

This study was aided by a grant from the Aaron W. Davis Foundation.
Read at annual meeting, American Urological Association, New York, N. Y. June 3, 1954.

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The presumed origin[14] of these patches in the female from epithelium of the urogenital sinus suggested the possibility that these foci in the urinary bladder might respond to estrogenic stimulation in a fashion similar to the well-known response of related mucosa in the reproductive tract. Reports[15, 16, 17, 18, 19, 20] of results of experiments in animals strengthen this hypothesis.

As far as can be ascertained, there are no reports indicating direct evidence of histological changes in the mucosa of the human urinary bladder following estrogenic stimulation. The following is a report of three cases in which changes in squamous patches in the mucosa of the trigone in women appeared to be related to the administration of estrogenic substances.

CASE REPORTS

Case 1. M. N., a 33 year old white woman, presented herself on September 12, 1949 with the chief complaints of difficulty of urination, frequency of urination, and pain following urination for 2 years. In September 1936, a partial resection of a cystic left ovary had been performed. In January 1939, the left tube, the remainder of the left ovary, and the right tube had been removed; the transcript of the findings at this operation stated that the right ovary was absent. One month before this latter operation, menopausal symptoms consisting of flushes, weakness, and nervousness began; these have continued until the present, although they are now somewhat less severe.

The general physical examination of September 12, 1949 was essentially negative. Urine examination revealed no abnormalities. Observation cystoscopy revealed a granular urethritis and a mild stenosis of the external urethral meatus. The bladder appeared normal. After a few dilatations of the urethra, the patient did not return; she was not seen again until October 1951. At that time, many cysts of the neck of the bladder were found on cystoscopy. The mucosa of the bladder, including the trigone, was normal. She was admitted to Lebanon Hospital on December 11, 1951. Culture of the urine was sterile. The cysts in the neck of the bladder from 9 to 3 o'clock were fulgurated under pentothal sodium anesthesia on December 12, 1951. At the same time, specimens of the trigone of the bladder were taken by biopsy, although no abnormalities could be seen. The report of the histological findings follows:

Sections revealed small fragments of mucosa from the urinary bladder. The epithelium was uniformly of the transitional type with flattened surface cells. There were no significant abnormalities of the lamina propria. Stains for glycogen revealed minimal amounts in the basal layer of the epithelium. Diagnosis: Normal mucosa of urinary bladder.

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The patient was discharged from the hospital on December 13, 1951. Therapy with premarin (2.5 mg. daily, orally) was begun on December 21, 1951. On January 4, 1952, a cystoscopy was performed in the office, and at this time four grayish-white, raised, granular patches could be seen on the trigone of the bladder, varying in diameter from 3–5 mm. Two of these were situated near the vesical neck to the right and left of the midline. Two others were situated just distal to the right and left ureteral orifices. There were a few cysts still present on the neck of the bladder between 5 and 7 o'clock.

Premarin was taken without interruption until admission to Lebanon Hospital on January 14, 1952. On January 15, 1952, under pentothal sodium anesthesia, specimens of the grayish-white patches on the trigone were taken by biopsy. The cysts of the vesical neck were now thoroughly fulgurated. The report of the histological findings follows:

Sections revealed fragments of mucosa from the urinary bladder containing areas of squamous epithelium. The latter was focal in distribution; the intervening epithelium was of the transitional type. The squamous epithelium was six to fifteen layers in width, and the superficial cells contained large perinuclear clear areas in which considerable amounts of glycogen were demonstrated by special stains. Foci of parakeratosis were noted. There appeared to be slight intraepithelial cornification. The lamina propria showed vascular engorgement and a slight infiltration by lymphocytes. Diagnosis: Fragments of vesical mucosa containing foci of squamous epithelium of the trigonal type (fig. 1).

Case 2. F. C., a white woman, 44 years of age, was first seen on December 8, 1950. Her chief complaint was increasing frequency of urination for 6 months; recently she had been voiding every half hour. One month previously (November, 8, 1950) her family physician had started her on premarin, 1.25 mg. daily orally because she had been complaining of hot flushes, nervousness and dizziness.

The patient had had a vaginal hysterectomy with a perineorrhaphy 10 years ago when she was thirty-four. The ovaries had not been removed. General physical examination disclosed essentially normal findings. Urine examination (catheterized specimen) showed only a rare leukocyte. On December 14, 1950, a cystoscopy was performed in Lebanon Hospital. A few cysts were present in the neck of the bladder, but the urethra, trigone and rest of the bladder showed no abnormalities. Cultures of urine from bladder and both kidneys were sterile.

Due to a questionable finding in the left pyelogram, it was decided to repeat the cystoscopy after an interval of several months. The patient had been taking premarin continuously for nearly 4 months; it had been stopped on March 1, 1951. A cystoscopy was performed on March 8, 1951. A left retrograde pyelogram was considered normal. A grayish-white, raised patch was observed on the trigone proximal to the neck of the bladder and distal to the right ureteral

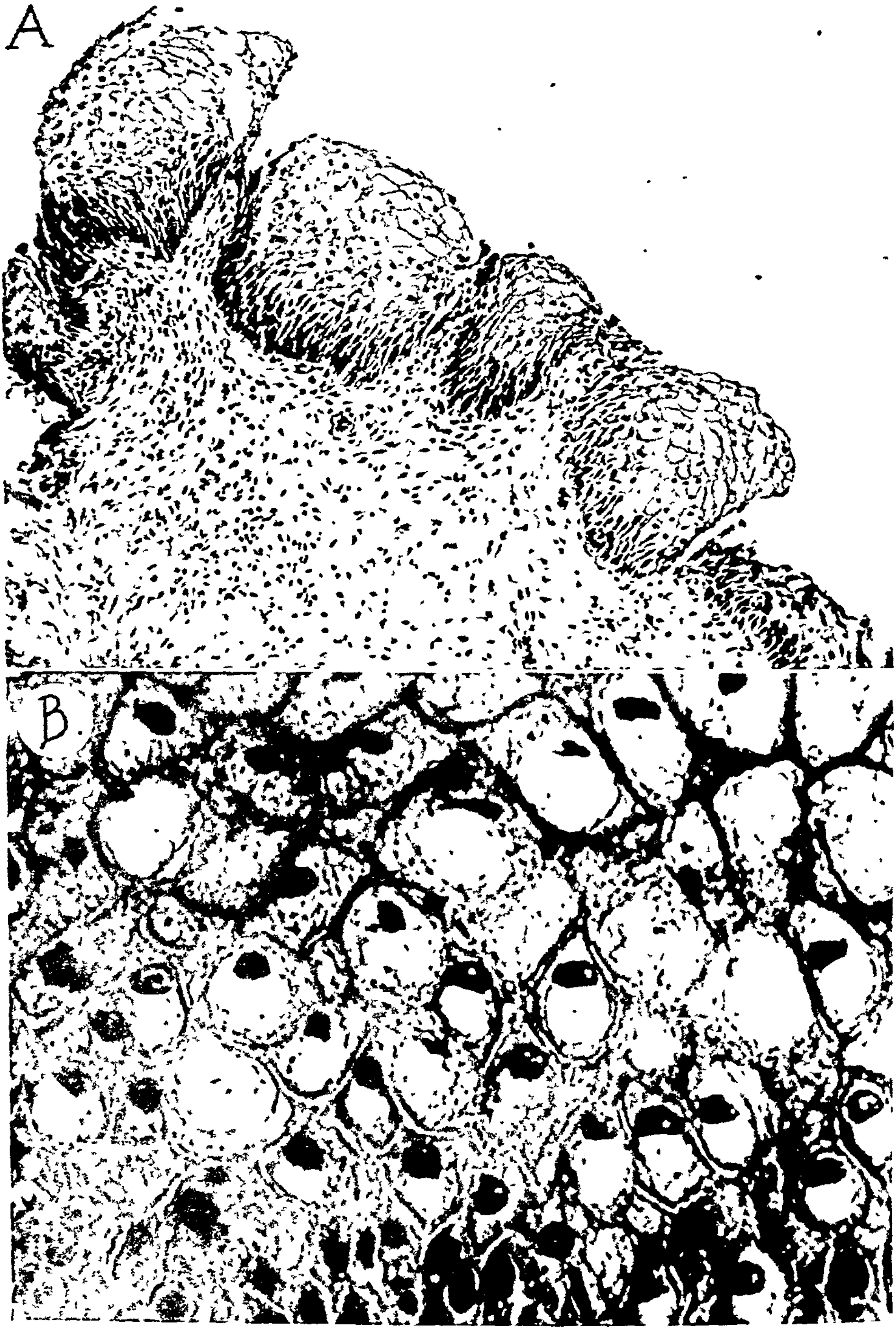

FIG. 1. Case 1. *A*, biopsy of trigone. Characteristic foci of squamous epithelium of trigonal type arranged in tiny plaques, some of which are connected by narrow bridges of transitional epithelium. Note festooned contour to basal zone of epithelium with intervening projections of lamina propria resembling papillary zone of dermis. Patient had been on estrogenic therapy. *B*, selected area from *A* at higher magnification to show gradual change in polarity from basal to superficial polyhedral cells. Note large, perinuclear clear areas and intercellular "canals"

orifice. It was about 5–7 mm. in diameter, smooth and glistening in appearance. A specimen was taken by biopsy from this area. The report of the histological findings follows:

Section revealed a fragment of mucosa from the urinary bladder. The lamina propria was covered by broad epithelium of the squamous type. The basal zone of the epithelium consisted of compactly arranged cells with dark nuclei, and was two to four layers in width. The polyhedral layer was three to eight rows in width, and many of these cells had large perinuclear, clear areas whose appearance suggested the presence of glycogen; this was confirmed by special stains. Normal epithelium of the transitional type did not appear in the specimen. Diagnosis: Fragments of vesical mucosa; epithelium entirely of squamous trigonal type (fig. 2, *A*).

The patient took no more estrogenic substances after March 1, 1951. She was readmitted to Lebanon Hospital on July 9, 1951. On July 12, 1951, cystoscopy was done under general anesthesia. Although no patch was seen in the trigone, five specimens were obtained by biopsy in the vicinity of the previous lesion. The report of the histological findings follows:

Sections revealed fragments of mucosa from the urinary bladder with foci of squamous epithelium appearing as patches or islands in otherwise normal transitional epithelium. These squamous foci were thinner than those in the specimen of March 7, 1951. The basal zone had two to four layers of cells, and the polyhedral layer also had two to four rows. Perinuclear vacuolization was much less conspicuous. Stain for glycogen disclosed minute amounts in the transitional epithelium; squamous foci did not appear in the fragments which had been placed in special fixative for glycogen stains. There was inflammation of the lamina propria. Diagnosis: Fragments of mucosa from the urinary bladder showing a few relatively thin foci of squamous epithelium (fig. 2, *B*).

Therapy with premarin, 1.25 mg. daily, orally was reinstituted on July 24, 1951, and was continued until re-admission to Lebanon Hospital on October 31, 1951. On November 1, 1951, a cystoscopy was performed. A raised, grayish-white, smooth, glistening mound, 3 mm. in diameter was observed in the same region as the original lesion. Specimens were taken from this area. The report of the histological findings follows:

The section consisted of three fragments of tissue from the urinary bladder. One of these was covered by relatively normal transitional epithelium. A second was covered partly by transitional and partly by squamous epithelium. A third fragment was covered entirely by squamous epithelium. The appearance of the squamous area was similar to that in the first specimen taken about eight months previously. Diagnosis: Fragments of mucosa from the urinary bladder containing foci of squamous epithelium of the trigonal type (fig. 3).

Case 3. M. B., a 49 year old white woman, came to the office on April 23, 1952, complaining of hematuria of 5 days' duration. The past history was noncontributory, except that for 2 years she had been going through the menopause and complaining of hot flushes, nervousness and irregular menstruation. Physical examination was essentially negative. Cystoscopy was performed at the office

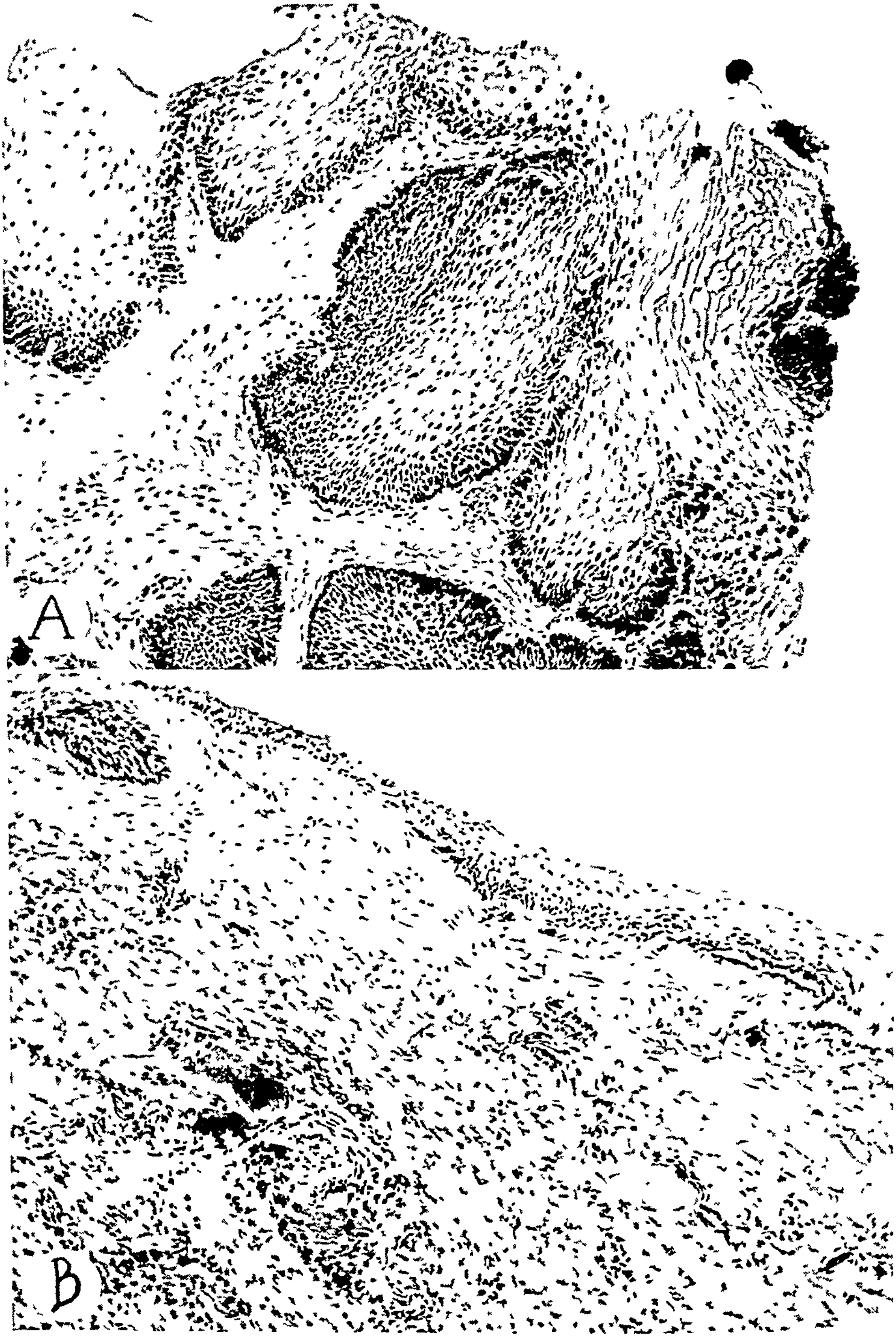

FIG. 2. Case 2. *A*, biopsy of trigone. Area illustrated is entirely covered by squamous epithelium of trigonal type. Patient had been on estrogenic therapy 4 months *B*, biopsy of trigone 4 months after cessation of estrogenic therapy. Area illustrated covered partly by transitional and partly by thinned out squamous epithelium. Inflammation of lamina propria.

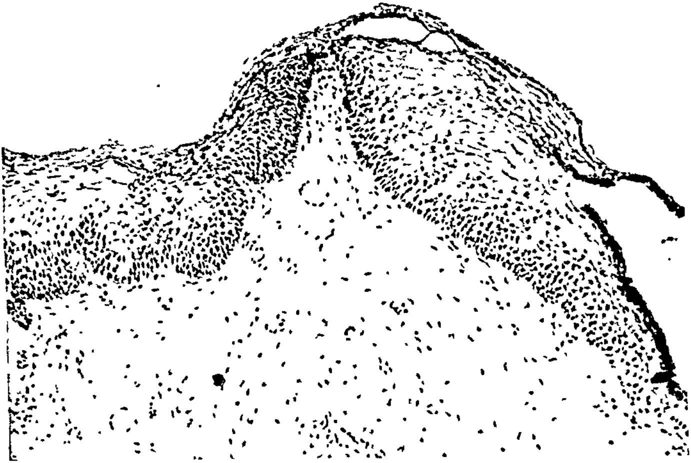

FIG. 3. Case 2. Same case as figure 2. Biopsy of trigone 3 months and 7 days after resumption of estrogenic therapy. Area illustrated covered entirely by squamous epithelium of trigonal type. Superficial layers of cells are compact, flattened, nonvacuolated with persistent nuclei and present appearance of parakeratosis.

and again in the hospital the following day. Just lateral to the right ureteral orifice was a 2–3 mm., papillomatous growth, with a thin stalk. The trigone was normal. Upper tracts were normal, and there was no growth on culture from either kidney or bladder. The patient was anesthetized with intravenous sodium pentothal. A specimen of the growth was taken by biopsy. The histopathological report was, "Fragments of papilloma of the urinary bladder; fragments of inflamed vesical mucosa." The remainder of the growth was then entirely fulgurated.

On July 15, 1952, specimens were taken from the trigone by biopsy, even though no abnormality was seen. The areas chosen were 0.5 cm. proximal to the vesical neck in the midline, and on the right side of the trigone, just distal to the ureteral orifice. The histological sections were read as follows:

Sections revealed small fragments of mucosa from the urinary bladder. The epithelium was uniformly of the transitional type. There were no significant abnormalities of the lamina propria. Diagnosis: Normal vesical mucosa.

On July 22, 1952, the patient was placed on premarin, 2.5 mg. a day. On August 12, 1952, cystoscopy was repeated. On the trigone in the midline, just proximal to the vesical neck, was a 3 mm., raised, white patch, with a fairly definite edge. Another patch similar to the above was present on the left side, just distal to the left ureteral orifice. Specimens were taken by biopsy, and the histological sections revealed the following:

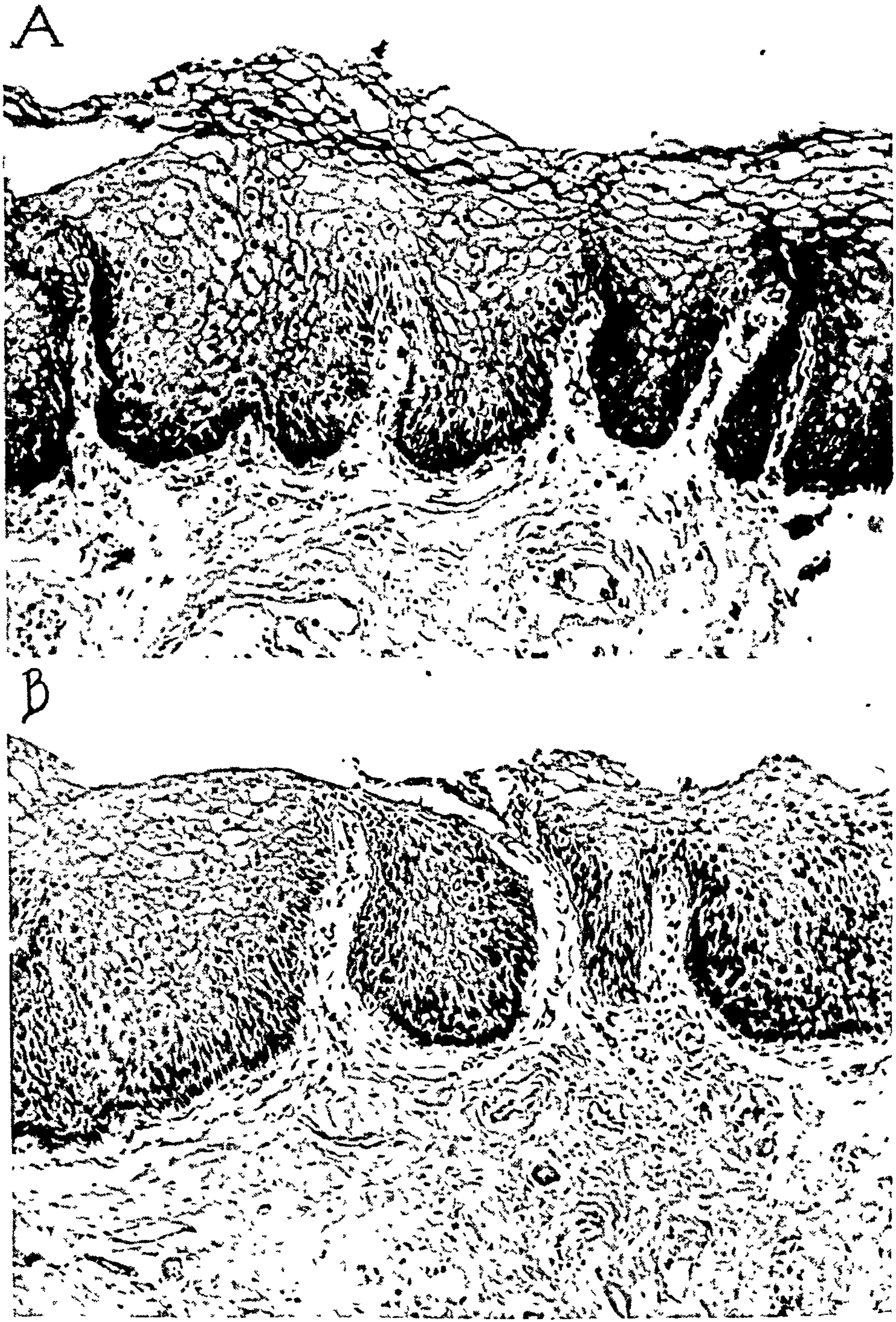

FIG. 4. Case 3. *A*, biopsy of trigone. Area completely covered by squamous epithelium of trigonal type. Patient had been on estrogenic therapy 3 weeks. *B*, biopsy of trigone after 2 years of almost continuous estrogenic therapy.

Most of the surface was covered by squamous epithelium of the [illegible] A few areas, however, were covered by transitional epithelium. The squamous epithelium was eight to twenty layers in width, and the superficial cells contained large perinuclear clear areas. Diagnosis: Fragments of vesical mucosa containing foci of squamous epithelium of the trigonal type (fig. 4, *A*).

Cystoscopies were performed at regular intervals with similar findings as aforementioned. She came to the office on April 6, 1954, and stated that she had taken premarin continuously until approximately 5 weeks ago. Cystoscopy revealed, just within the vesical neck, several white patches, measuring 3 by 5 mm. Specimens were taken by biopsy. The histological findings follow:

One of the fragments was covered by transitional epithelium. The others were completely covered by squamous epithelium of the trigonal type. The foci of squamous epithelium were arranged in mosaic fashion. These foci were larger than those in the previous specimen. There were more layers of cells, and the perinuclear clear zones were more conspicuous indicating greater amounts of glycogen; this was confirmed by special stains. There appeared to be a slight degree of surface keratinization. In other areas of the same specimen, perinuclear clear areas were less conspicuous. Diagnosis: Fragments of mucosa from the trigone containing foci of squamous epithelium of the trigonal type (fig. 4, *B*).

She was placed on premarin, 2.5 mg. orally, 3 times a week and 50,000 units of

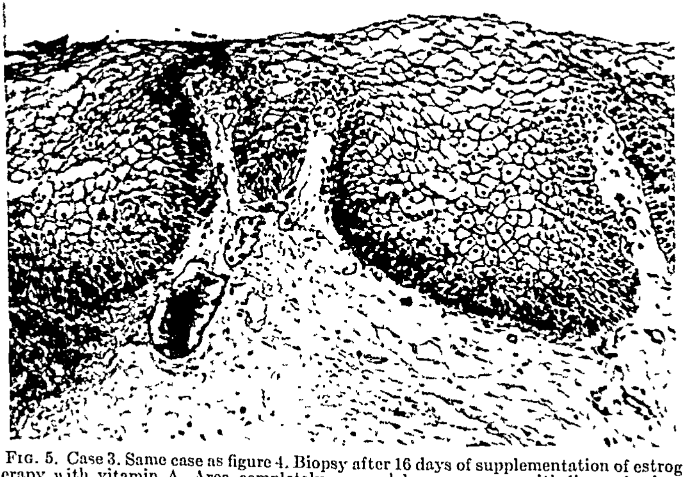

Fig. 5. Case 3. Same case as figure 4. Biopsy after 16 days of supplementation of estrogen therapy with vitamin A. Area completely covered by squamous epithelium of trigonal type. Note appearance of keratinization in superficial cells above at left and suggestion of intra-epithelial cornification above, at right.

vitamin A[21, 22] orally per day. On April 22, 1954, cystoscopy was repeated and the patches on the trigone were the same as previously described. Biopsies were taken from just within the vesical neck. The histological findings were similar to those 16 days previously. Diagnosis: Fragments of vesical mucosa containing foci of squamous epithelium of the trigonal type (fig. 5).

Sections of specimens from this case were examined for alkaline phosphatase;[23] there was none found in the epithelium.*

GENERAL SUMMATION OF HISTOLOGICAL FEATURES OF SQUAMOUS EPITHELIUM IN THE HUMAN FEMALE TRIGONE

Histological sections of these areas reveal stratified epithelium of the squamous type with certain special features. The large cells in the upper layers are polyhedral in form and contain a small, dark nucleus, surrounded by a large perinuclear clear space; the latter, in special stains, is found to have a rich content of glycogen. The nuclei are clearly visible all the way to the surface. There are no intercellular bridges; however, the large clear cells in the superficial layers appear to be separated from one another by an interlacing system of "canals" of uniform width with thin, brightly staining walls closely applied to or forming part of the cell membrane (fig. 1). "Intra-epithelial cornification" has been described and has been considered similar to that observed in the vaginal mucosa by Dierks[24] and Smith.[25] The squamous epithelium in the trigone is broader than the transitional epithelium of the urinary bladder and is characteristically arranged in tiny, disc-shaped plaques, which are closely apposed to one another in mosaic fashion (figs. 1, *A*, 2, *A*, 4, *A*, 4, *B*, 5). Occasionally, these plaques are connected by narrow bridges of transitional epithelium (fig. 1, *A*). The result is a distinctive festooned or scalloped contour of the basal layer of cells in relation to the lamina propria. It is this last feature which distinguishes the squamous epithelium of the human female trigone from vaginal mucosa. We have designated this epithelium "squamous epithelium of the trigonal type" because of the special characteristics mentioned.

SUMMARY AND CONCLUSIONS

Observations are reported on three women, who presented distinctive grayish-white patches on the trigone of the urinary bladder. The histological appearance of all these areas was that of squamous epithelium.

Our study of extensive postmortem and surgical material confirms the contention of Cifuentes[12] that foci of squamous epithelium constitute an anatomi-

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* These studies were kindly performed by Dr. Max Wachstein.

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cally distinctive feature of the human female trigone Cystoscopic observations by one of us (C N) suggest that increased and/or prolonged therapy with estrogens may expand these foci, conversely, they may diminish in size after cessation of estrogenic therapy

The presence of presumably estrogen sensitive squamous epithelium in the trigone has to be evaluated in relation to the changes in exfoliated cells in the urine during pregnancy[26] and the menstrual cycle[27, 28, 29]

It is of practical value for the cystoscopist to be aware that the grayish white patches on the trigone herein described occur normally in the human female trigone and are composed of squamous epithelium

The distinguishing histological characteristics of this epithelium are described, the designation, "squamous epithelium of the trigonal type" is suggested

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ADENOCARCINOMA ARISING IN EXSTROPHY OF THE BLADDER: REPORT OF TWO CASES AND REVIEW OF THE LITERATURE

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Of all the congenital deformities, exstrophy of the bladder is one of the more uncommon ones. The deformity is said to occur once in every 50,000 births, according to Neudorfer. Of these cases it can be estimated that only 33 per cent of untreated individuals will be alive at age 20. This figure of survival rate is reported to be somewhat improved if reparative surgery has been performed. Upper urinary tract infection, with the associated lesions and resulting damage, is by far the leading cause of death. A review of the admissions to the University Hospitals since 1925 produced but 25 cases of bladder exstrophy.

A complication of considerable rarity in bladder exstrophy is the development of a malignant neoplasm. To date there have been 38 cases reported in the literature, and these cases are reviewed with this paper. The purpose of this report is to present two additional cases.

It is of interest to note that the malignancy was classified as an adenocarcinoma in 33 of the cases, a squamous cell carcinoma in two of the cases, while the classification was not designated for five. Thus, of the 35 cases in which the classification is stated, the adenocarcinoma is the type of neoplasm in 94 per cent. In view of the transitional cell lining of the bladder, this occurrence of adenocarcinoma would seem paradoxical. However, a study of the histological changes occurring with passage of time in the exstrophied bladder helps to explain the occurrence of a glandular neoplasm, and this will be discussed later.

CASE REPORTS

Case 1. S. K., No. 2005, a 36 year old patient, was first admitted to University Hospitals in April 1925. Physical examination revealed a typical exstrophy of the bladder with associated epispadias. The testes were present in the scrotum. X-rays revealed left hydronephrosis with calculi, and there was also a small calculus in the left ureter. The patient refused any form of therapy either for his kidney or for his exstrophy of the bladder.

The patient was next seen in University Hospitals in March 1945, seventeen years later, with the chief complaint of bleeding from the exstrophied bladder. He was 54 years of age at that time. He still had received no surgical therapy for the exstrophy. A biopsy of the bladder was performed, and this revealed an adenocarcinoma. On March 26, 1945 total cystectomy and bilateral cutaneous ureterostomy were performed, and the patient recovered satisfactorily. X-rays of the kidneys during this admission revealed a staghorn calculus in the left kidney and a small calculus in the lower pole of the right kidney. A chest x-ray and abdominal exploration at the time of surgery both failed to reveal any evidence of metastases.

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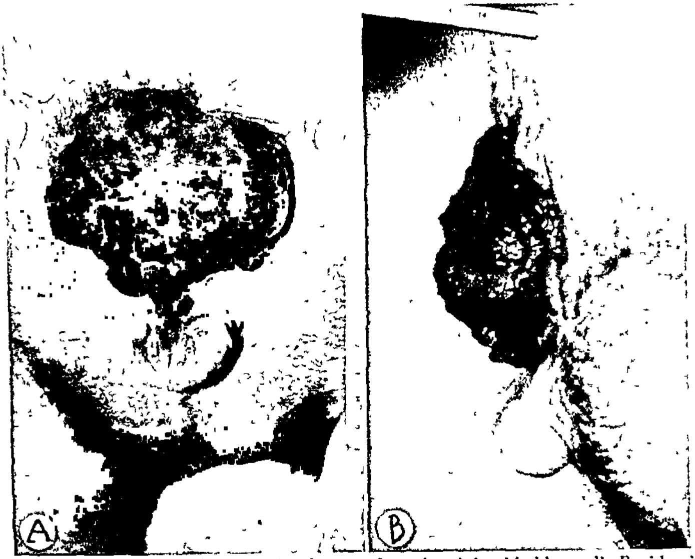

FIG. 1. Case 2. *A*, anterior view showing neoplasm involving bladder wall. *B*, side view demonstrating piling up of neoplastic tissue.

He was later seen at this hospital in October 1945 at which time a check-up revealed no evidence of metastasis.

A report from the home town physician reveals that the patient, in a semi-comatose condition, was admitted to the local hospital on August 6, 1947 and that he died 5 days later. The nonprotein nitrogen was reported to be 120 mg. per cent. Death was attributed to uremia and an infected urinary tract. There was no evidence of recurrence of his bladder carcinoma.

Case 2. E. S., No. 288432, a 35 year old white man, was admitted to the University Hospitals in March 1953.* His chief complaint was that bleeding had developed in the exstrophy 6 weeks prior to admission. He noticed the development of a large mass forming over the bladder mucosa. The bleeding seemed to come from this point. Physical examination was essentially negative except for the exstrophy and associated epispadias (fig. 1). There was a large, friable, red, oozing mass present over the bladder mucosa with the exception of the region of the trigone. The testicles were present in the scrotum.

Chest x-ray failed to reveal a pulmonary disease. Excretory urogram showed right hydro-ureter and hydronephrosis.

The patient was treated in the usual fashion by transplanting his ureters to

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* A biopsy performed on February 11, 1953 by Dr. William A. Dafoe of Appleton, was sent to the State Laboratory of Hygiene, and this specimen revealed adenocarcinoma.

We are indebted to Dr. Dafoe and Dr. Chris P. Arnoldussen of Fremont for sending the patient to the University Hospitals for further study and treatment the sigmoid in two procedures; and in June 1953 a total cystectomy was performed without incident. He demonstrated poor and slow wound healing. Other than that his recoveries were without incident.

The surgical specimen revealed adenocarcinoma in the lateral walls of the bladder. No evidence of metastasis was noted during any of the surgical procedures.

This patient is now home, working, and feeling well approximately one year after surgery.

DISCUSSION

An examination of the total of 40 cases reveals several interesting observations. The carcinomas occurred in males in 25 cases (64 per cent) and in females in 14 cases (34 per cent); the sex was not mentioned in 1 case. This is of interest when it is considered that the anomaly of exstrophy of the bladder itself is 5 to 7 times more common in males. The average age at the time of diagnosis was 44, the youngest case being 21.

It is also worthy to note the lack of apparent metastases in these cases. In only one instance, a case reported by Scholl, were metastases described, and in this patient death was attributed to the metastases. Other authors have listed the case of Lower in 1921 as succumbing to metastasis, but in the original article no mention of a fatal outcome can be found. Thus, all evidence to date demonstrates a slow progression of carcinoma in an exstrophy and a very low rate of metastasis.

Mention has already been made of the preponderance of adenocarcinoma as the type of malignant neoplasm usually occurring in patients with the anomaly being discussed, while adenocarcinoma is the unusual type of neoplasm in the normally developed bladder. In most series of carcinoma of the bladder (in the absence of exstrophy) the percentage that is of glandular type is reported to be only 1–2 per cent. Therefore, much interest and speculation have arisen to explain the difference in prevalence of adenocarcinoma in the two groups of individuals, that is, those with exstrophy and those without this anomaly. It is, then, of interest to consider the source of the glandular tissue from which the adenocarcinomas arise.

There are different theories attempting to explain the source of glandular tissue in the bladder, particularly the exstrophied bladder; these possible sources are listed as follows:

A) Embryonic residuals of the urachus.

B) Glandular tissue that is normally present in many bladders.

C) Maldevelopment in the division of the cloaca resulting in deposition of the lining cells of intestinal type in the bladder wall.

D) Metaplasia of transitional epithelium.

Before discussing each theory, a brief review of the embryological steps as described in Arey's *Developmental Anatomy* will be of value.

The nephrotome from which the upper portion of the urogenital system develops is mesodermal in character, whereas the lower urinary tract is entodermal in origin. The urological junction of mesodermal and entodermal tissues is in the bladder. The original embryological kidney, the pronephros, is absorbed by the mesonephros and the pronephric duct is retained as an excretory tube known as the mesonephric or wolffian duct. By the tenth fetal week the mesonephric kidney is rapidly being replaced by the metanephric or final kidney. This metanephric kidney is developed from a bud from the distal end of the mesonephric duct, and thus a new excretory duct is formed in the process. The mesonephric duct in the female then undergoes atrophy and in the male subsequently develops into the vas deferens and ejaculatory duct.

With further fetal development the cloaca, of entodermal origin, divides into the bladder and rectum. The segment of tissue which contains the closely associated openings of the metanephros (ureters) and of the mesonephros (vasa) is incorporated in the bladder development and forms the future trigone, posterior urethra, and prostate. Thus, the trigone and posterior urethra are mesodermal in origin while the remaining portion of the bladder is of entodermal origin, including the urachus.

In attempting to form an opinion concerning the origin of adenomatous tissue we next examined the records of cases at this hospital. Of the 25 cases of exstrophy, thirteen had cystectomies, and two of these were the cases of carcinoma reviewed above. Review of the slides of the other eleven cases ranging in age from 1 to 19 showed cystic changes with columnar type of cells in all of the cases. A search for autopsies of newborn infants with exstrophy revealed no cases at the University Hospitals. However, examination by Enderlen and Formiggini of newborns with exstrophy failed to reveal any glandular tissue present in the bladder mucosa.

Another fact is worth noting also. The location of adenocarcinomas in the normally developed bladder is predominantly in the region of the trigone, while in exstrophy the neoplasms are usually peripheral in origin.

With the benefit of this information it is now possible to examine each theory more carefully.

A. Urachal origin of glandular epithelium. Adenocarcinoma of urachal origin has been reported in the fundus of normal bladders occasionally, and these are usually characterized as colloid in type. They are localized to the superior portion of the bladder and are uncommon. In an exstrophy the adenomatous elements are found throughout the bladder wall, and the neoplasms also have not been noted to be localized in any portion of the bladder.

B. Normally present glandular tissue. Albarran in 1892 first described the subtrigonal glands in the bladder that are associated with his name. Virchow maintained that these glands represented aberrant prostatic tissue while Aschoff felt that they came from the posterior urethra. Scholl, in 1922, contended that carcinoma in an exstrophy develops from these glands. Most investigators will concur that glandular tissue in small amounts is frequently found in the trigone but doubt that this tissue represents the source of neoplastic change in bladder exstrophy because the majority of neoplasms in such bladders arise laterally. Emmett, in a 1942 study, was impressed with the relative scarcity of these glands and questioned their importance in the development of cystitis cystica.

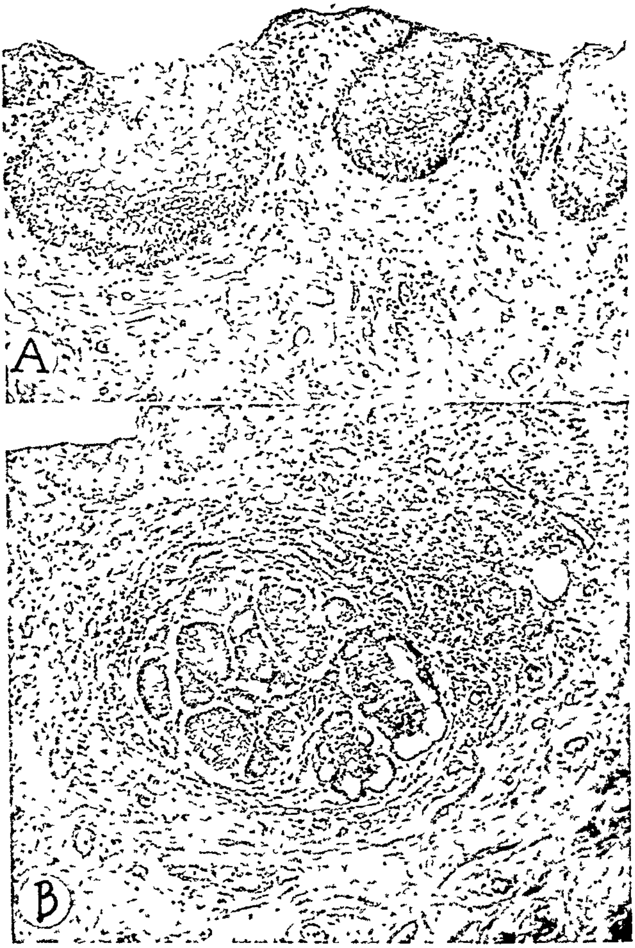

FIG. 2. *A*, from case of exstrophy of bladder that had not undergone malignant change. Low power photomicrograph showing invagination of mucosa. *B*, from case of exstrophy of bladder with no neoplastic involvement. Low power photomicrograph showing epithelial nest. Note columnar epithelium developing.

Glandular structures have been noted by various authors to be found outside the trigone in the entodermal portion of the bladder. Begg, and later Saphir and Kurland, described such glands. Von Mollendorf and Morse both stated that above the trigone glandular structures were not normally found and any that were present represented inflammatory changes. This theory was originated by von Brunn who believed that with inflammation the deeper layers of epithelium became pinched off forming structures now referred to as "Brunn's nests." He thought that these nests might then develop into cystic structures.

Thus, no author has strongly supported the concept of glandular tissue being normally present in the bladder except in the trigone.

C. Inclusion of intestinal type of epithelium. In a normal individual, in addition to the division of the cloaca into bladder and rectum, epithelial changes occur during embryologic development. The cells lining the bladder form a transitional type of epithelium while the mucosa of the rectum is made up of glandular epithelium. Ehrich in 1901 suggested that occasionally remnants of rectal mucosa are found in normal bladders. He was of the opinion that epithelium destined to be rectal mucosa became pinched off in the division process and continued its development in the bladder wall. Subsequently other authors, Hovelacque, Lacene, Judd, Thompson, and Hache also have mentioned this theory as a possible explanation for the development of adenomatous epithelium in exstrophied bladders.

The strongest evidence supporting this theory appears to be that the adenomatous epithelium in the walls of exstrophied bladders histologically closely resem-

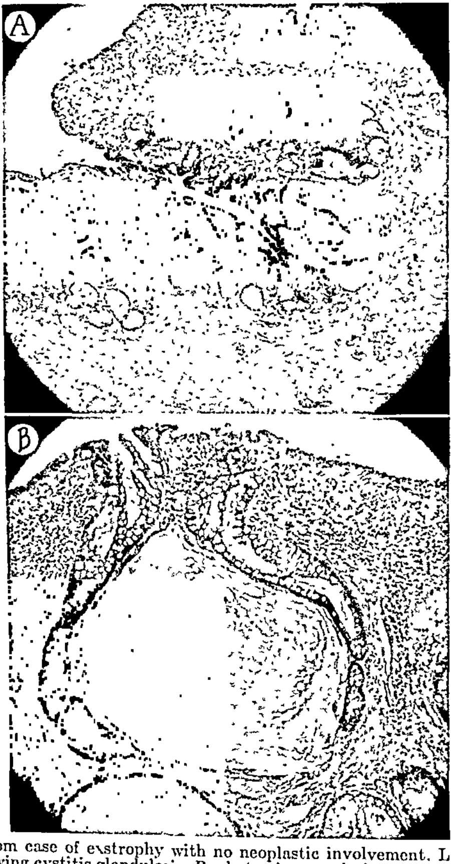

FIG. 3. *A*, from case of exstrophy with no neoplastic involvement. Low power photomicrograph showing cystitis glandularis. *B*, photomicrograph showing goblet cells and pool of mucus within cystic gland in case of exstrophy of bladder.

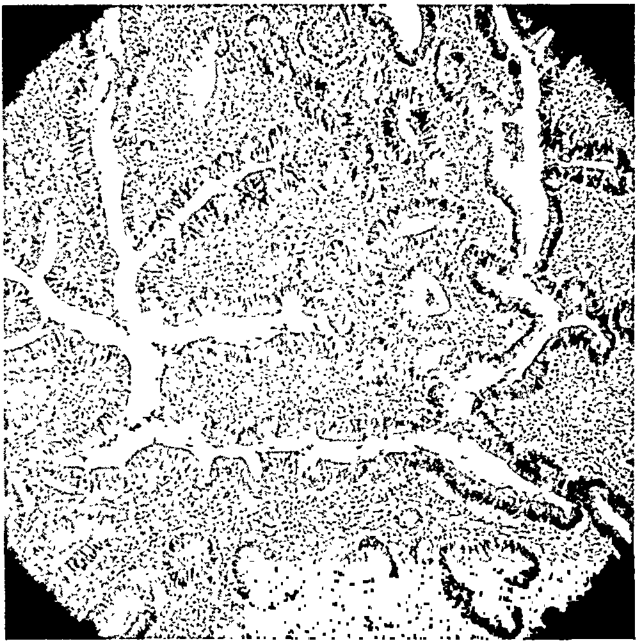

FIG. 4. Case 1. Low power photomicrograph showing adenocarcinoma in exstrophy of bladder.

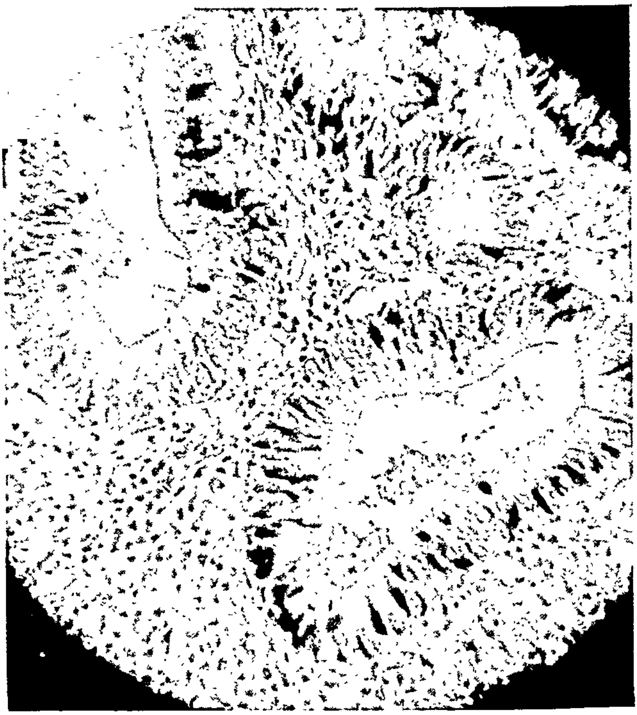

FIG. 5. Case 1. High power photomicrograph showing mitotic figures in glandular epithelium.

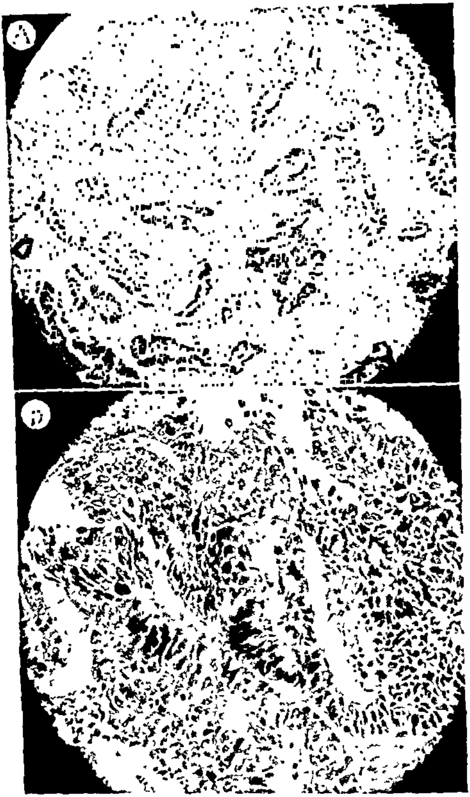

FIG. 6. Case 2. Adenocarcinoma in exstrophy of bladder. *A*, low power photomicrograph. *B*, high power photomicrograph.

bles that of rectal mucosa. However, a histological study of exstrophied bladders reveals a gradual change from a transitional to a columnar type of epithelium with mucus formation. Scattered through the bladder wall are simple infoldings of epithelium, cysts, and glandular elements which appear to represent various stages of a process in transition rather than an embryological defect.

D. Metaplasia. When the word, metaplasia is used it usually connotes a change of epithelium to squamous type. The reference in this case is to the change of transitional epithelium to adenomatous type. It is believed by many authors that the epithelium from the cloaca that forms the mucosa of an exstrophied bladder is destined to become transitional epithelium but because of the anomaly reverts back to adenomatous type. Some think that this process occurs because the bladder fails to develop into a reservoir. Pund, et al. in 1952 suggested that this was an arrested function and that when epithelium is devoid of its normal function, it reverts to a previous form. In this instance this would mean returning to adenomatous epithelium present as the cloacal lining.

Another variation of this same theme involves the factor of inflammation. Chronic inflammation is ever present in exstrophied bladders as the result of exposure. Schridde and later Karsner used the term prosoplastic metaplasia in explaining their theory of cell differentiation as a result of chronic inflammation in normal bladders. Pincsohn wrote of "indirect metaplasia" in attributing the development of columnar cells. He suggested that the dominant tissue cell becomes inferior to recessive cells in the presence of inflammation. Thus, the recessive columnar cell in areas becomes dominant to exchange with the transitional cell.

Von Brunn, aforementioned, was the first to write of the effects of irritation and infection on bladder mucosa. Subsequent authors, Zuckerkandl, Patch, Rhea, Scholl, and Morse have agreed with this, but there is some disagreement as to whether these nests develop lumina by degeneration of the center or by secretion of newly-developed goblet cells. These authors have carried Von Brunn's theory further; they believe that from cell nests develop cysts known as cystitis cystica and that stimulus of further irritation and infection usually change these cysts into glands known as cystitis glandularis. From this stage it is believed that adenocarcinoma may arise. More recently this was pointed out in detail by Melicow.

In exstrophy the irritation is tremendous and constant. We found cystitis cystica and glandularis in 100 per cent of exstrophied bladders biopsied at this hospital. A final point of evidence for this theory would seem to lie in the findings within exstrophied bladders of newborn infants, for if these glands are lacking in the newborn this would lend credence to the environmental explanation. Only a few such postmortem studies of newborns have been published and as previously stated were reported not to have columnar epithelium present.

It is our opinion that this theory best explains the majority of the cases. Figures 2 and 3 are photomicrographs taken from representative sections of exstrophic bladders with no neoplastic change. Figure 2, *A* shows the infolding of the transitional epithelium with a nest forming in figure 2, *B*. Figure 2, *B* shows the epithelium becoming columnar with formation of acini. Figure 3, *A* shows cystitis glandularis and typical adenomatous epithelium. Figure 3, *B* shows goblet cells and a pool of mucus within a cystic gland. Figures 4 and 5 are representative low and high power photomicrographs of case 1. Figure 6 is from case 2.

SUMMARY

Twenty-five cases of exstrophy of the bladder were seen at the University Hospitals since 1925.

Of these, 2 cases were complicated by adenocarcinoma.

A study was made of the previously reported 38 cases of exstrophy complicated by malignancy; and these cases, with the two presented in this paper, were analyzed briefly.

Of these 40 cases a vast majority were diagnosed histologically as adenocarcinoma rather than transitional cell type usually found in the normally developed bladder.

The literature concerning the etiology of adenomatous epithelium in the bladder has been reviewed The different theories were presented and discussed The prevailing opinion at the present time is that the exposure of the exstrophied bladder to the environment and constant infection stimulates the mucosa to alter its type in areas, possibly to produce protective mucus All cases of exstrophied bladder that were subjected to biopsy at this hospital revealed cystitis cystica and glandularis

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FURTHER STUDIES ON ABSORPTION THROUGH THE HUMAN BLADDER

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Two cases occurred which were ideal for study of absorption through the human bladder. It was desirous to check and extend the studies on the unique case previously presented by the writer (1953). The two patients in the present report (VAH 34119 and 35210) had undergone abdominoperineal resection of the rectosigmoid for carcinoma of the rectum. After some months they were re-admitted with dyspnea, nausea, vomiting, generalized edema, oliguria, uremia, advanced acidosis, and hyperkalemia. Cystoscopy disclosed bladders with practically normal lining and no invasion by tumor. There was advanced bilateral hydronephrosis owing to near-complete low ureteral obstruction. These findings, together with the known history of the patients, permitted one to diagnose bilateral ureteral obstruction secondary to extension of adenocarcinoma of rectum. The immediate preoperative serum [K^+] was 7.5 and 9.5 mEq., respectively. Life-saving palliative cutaneous ureterostomy was performed in both patients under spinal anesthesia. Diuresis set in promptly after release of the ureters from obstruction and the postoperative course was smooth. Urinary drainage was through 18F whistle-tip latex catheters in the dilated ureters. The studies extended from 6 weeks to 4 months post-ureterostomy, at the lapse of which time re-cystoscopy showed no invasion of bladder lining by tumor.

METHODS

Essentially the same technique, with U-shaped mercurial manometer to provide a mobile system, was used as previously (Maluf, 1953). A 20F urethral balloon catheter, with its balloon inflated with 10 cc, was used. The accuracy of return of liquid, after injecting air into the bladder and re-aspirating, was within 0.5 cc. Less liquid was introduced into the bladder than the latter could hold with discomfort. Neither patient underwent vesical spasm. As in the past, analyses of the initial and final concentrations were always run concurrently to cancel differences produced by slight errors of analytical technique.

RESULTS

1) *Absorption of sodium and chloride from an isotonic solution of sodium chloride.* A known volume of isotonic NaCl solution (Abbott) was introduced into each bladder. After the lapse of 4 hours the volumes in the bladder were unchanged and the alterations in total Na^+ and Cl^- in the bladder were within the limits of error (table 1). The previous finding (1953) that there is practically no net absorption of water, Na^+, or Cl^- from an isotonic solution of NaCl was thus confirmed.

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TABLE 1

	Vol (cc)	Total mEq in bladder	
		Na⁺	Cl⁻
VAH 34119			
Initial	100	15.5	15.0
Final	100	15.1	14.8
Difference	0	−0.4	−0.2
VAH 35210			
Initial	202	31.7	29.8
Final	202	32.2	29.4
Difference	0	+0.5	−0.4

TABLE 2

	Vol (cc)	Total mEq in bladder	
		Na⁺	Cl⁻
VAH 34119			
Initial	100	46.5	42.0
Final	113	42.0	38.5
Difference	+13	−4.5	−3.5
VAH 35210			
Initial	170	74.8	69.0
Final	182	74.0	58.2
Difference	+12	−0.8	−10.8

2) *Absorption of sodium and chloride from a hypertonic solution of sodium chloride.* Roughly 2.5 per cent NaCl in water was prepared and autoclaved. After a lapse of 4 hours it was found that water had been absorbed into the bladder; there had been a net loss of Cl^- and a small to negligible loss of Na^+ (table 2). This confirms the previous findings.

3) *Absorption of potassium.* Roughly 2 per cent KCl in water was prepared and autoclaved. A "run" of 4 hours (table 3) confirms the previous finding that potassium does not diffuse through the bladder, even from a moderately hypertonic solution (1.21 per cent is isotonic with plasma). The changes in the table are within limits of error. Water enters the bladder, as would be expected, with a hypertonic solution of slowly diffusible electrolyte.

4) *Absorption of urea.* A somewhat hypotonic (1.5 per cent) solution of urea in water was used (1.8 per cent is isotonic with plasma). Urea diffused out of the bladder and so did some water (table 4). This supplements our previous findings with a somewhat hypertonic solution of urea.

The table gives the amount absorbed in 4 hours. The hourly rate ranged between 35 mg. and 80 mg. The single value of 56 mg. per hour, obtained in the previous work using a somewhat hypertonic (1.95 per cent) solution, is of the same order.

5) *Absorption of dextrose.* Dextrose 5 per cent in water (Abbott) was introduced into each bladder in a 4-hour "run", 4 times, and showed no appreciable

TABLE 3

	Vol (cc)	Total mEq in bladder	
		K^+	Cl^-
VAH 34119			
Initial	100	28.0	26.5
Final	108	29.0	28.2
Difference	+8	+1.0	+1.7
VAH 35210			
Initial	170	45.0	42.3
Final	182	46.7	41.8
Difference	+12	+1.7	−0.5

TABLE 4

	Vol (cc)	Total Gm in bladder
VAH 34119		
Initial	100	1.52
Final	98	1.33
Difference	−2	−0.19
Initial	100	1.56
Final	89	1.24
Difference	−11	−0.32
VAH 35120	170	2.78
Initial	168	2.58
Final	−2	−0.20
Difference		
Initial	170	2.62
Final	169	2.48
Difference	−1	−.14

alteration in volume. The variation in total amount of dextrose was within the limits of error (± 0.5 gm./100 cc).

6) *Glycine 1.2 per cent in water.* This solution was tried because we use it for irrigation in transurethral electroresection of the prostate. It was introduced for this by Nesbit and Glickman (1948) who noted that 2.1 per cent glycine is isotonic with the plasma but that 1.1 per cent, while hypotonic, is not hemolytic *in vitro* or *in vivo*.

There was no appreciable change in volume in two "runs" of 4 hours with each bladder. The glycine concentration was not measured. The augmentation in weight of a patient undergoing transurethral electroresection of the prostate, as our former senior resident Dr. Robert S. Hagstrom* has shown, is due to entry of irrigating liquid through open blood vessels of the prostate.

7) *Absorption of urokon* (Na 3-acetylamino-2,4,6-triiodobenzoate). Urokon 70 per cent (Mallinckrodt) 96 cc and 170 cc were introduced into the bladder of VAH 34119 and VAH 35210, respectively, in the same manner as for the other solutions. Fluids were withheld as of only 3 hours before the experiment. At 4

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* *Note by editor* See report by Dr. Hagstrom, pp. 852–859, this issue.

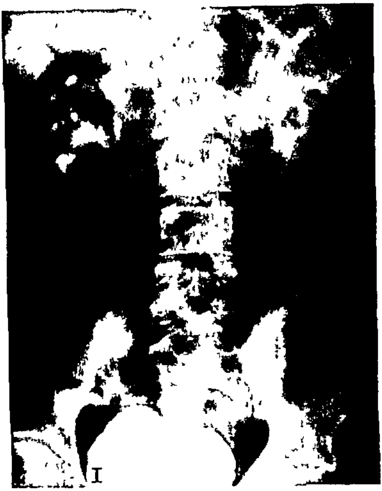

Fig 1. Pyelogram obtained by introduction of 96 cc 70 per cent urokon into bladder of patient (VAH 34119) with bilateral cutaneous ureterostomy. Radiopaque shadow in pelvis is bladder containing urokon.

hours the urethral catheter was clamped and a radiogram of the abdomen taken. Excellent pyelograms of both kidneys were thus obtained in both patients (fig. 1). No radiopaque substance was administered in any other way. Frey (1932) depicted radiographic evidence of absorption of other organic iodides through the bladder of rabbits.

8) *Absorption of sodium iodide.* Ten per cent NaI in water 100 cc and 120 cc were introduced into the bladder of VAH 34119 and VAH 35210, respectively. The patients were minimally dehydrated, as for the absorption of urokon. Radiograms of the abdomen at 4 hours disclosed radiopacity of the latex ureteral catheters, which were otherwise radiolucent, but only exceedingly faint pyelograms. Osborne et al. (1923) were the first to demonstrate that adequate pyelograms can be obtained from 10 gm. NaI administered intravenously. Schär (1938) and Lundberg (1929) showed, by direct analysis, that iodide is absorbed through the human bladder from NaI and LiI, respectively. Frey (1932) found marked absorption of NaBr from the bladder of rabbits. The writer has shown that another halide, namely Cl^-, is appreciably absorbed through the human bladder if in high enough concentration.

9) *Absorption of water.* In the final experiment 100 cc plain water were introduced into the bladder of VAH 34119 and 120 cc into that of VAH 35210. After 4 hours only 94 cc and 112 cc could be recovered, respectively.

DISCUSSION

The results confirm and extend a previous report by the writer (1953). The simplest hypothesis which accommodates all the data is that absorption through

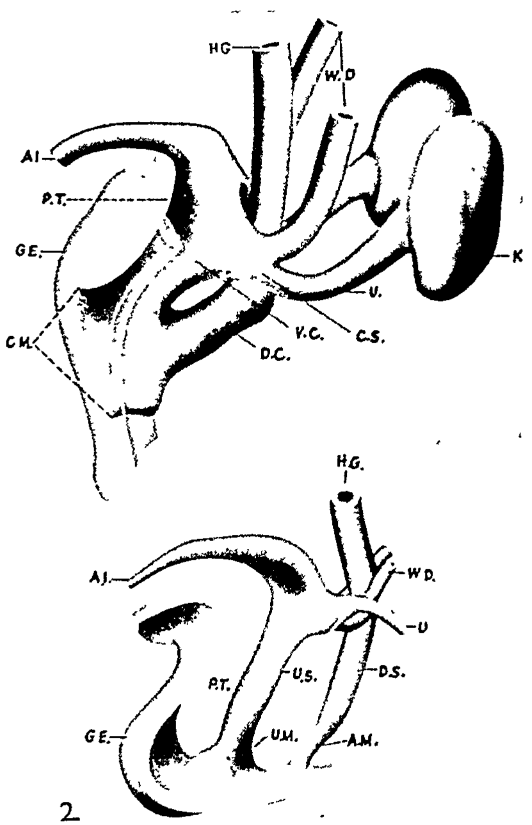

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FIG. 2. Two stages in division of human cloaca. Upper figure is from 12 mm. embryo and the lower from a 16 mm. embryo in which division of cloaca has been completed. *A.I.* allantoic stalk; *A.M.* position of anal membrane; *C.M.* cloacal membrane; *C.S.* cloacal segment of wolffian duct; *D.S.* dorsal segment (rectum) of partitioning cloaca; *G.E.* genital eminence; *H.G.* hind gut; *K* kidney; *P.T.* precloacal mesodermic tissue; *U* ureters; *U.M.* position of urogenital membrane; *U.S.* bladder-urogenital sinus; *V.C.* ventral segment (bladder-urethra) of partitioning cloaca; *W.D.* wolffian ducts. (After Pohlman, 1911.)

the bladder occurs by simple diffusion and that the bladder is, happily, a rather poorly permeable "membrane." Thus, the low rates of absorption through the bladder may be contrasted sharply with absorption in 3 hours of all the 150 cc of water introduced into the human rectosigmoid (Annis, 1952) and absorption in 2 hours of 40 per cent of the water and 52 per cent of the chloride from 300 cc of 0.9 per cent NaCl in a segment of human right colon (Moore, 1953).

The cloaca of the human embryo, at the age of 4 to 5 weeks (5 mm.), begins to divide by downgrowth of a urorectal septum. At the age of about 7 weeks (16 mm.) division of the cloaca into bladder-urethra and rectum becomes complete (fig. 2). The linings of bladder and of rectum subsequently differ markedly from each other. The lining or epithelium of the former is composed of stratified cuboidal, apparently nonglandular cells whereas that of the latter is made of crypts of columnar, glandular cells. The rectosigmoid and colon can actively absorb Na^+ and Cl^- against concentration gradients and can actively release K^+ and HCO_3^- into the lumen even when the latter are more concentrated in the lumen than in the plasma (Annis, 1952; Moore, 1953; Scribner et al., 1953; Field et al., 1954).

SUMMARY

Two patients with normal bladder lining and with palliative bilateral cutaneous ureterostomy formed the subjects of this study

There was no appreciable net absorption of Na^+, Cl^-, and water through the bladder from an isotonic solution of NaCl

Na^+ and Cl^- were absorbed through the bladder from hypertonic NaCl Water simultaneously entered the bladder

There was no significant net absorption of K^+ or Cl^- through the bladder from moderately hypertonic KCl

Urea was absorbed appreciably through the bladder from a hypotonic solution of urea Water was simultaneously absorbed from the bladder

Dextrose is not appreciably absorbed through the bladder

Water is not absorbed appreciably from moderately hypotonic glycine

Urokon (Na 3-acetylamino-2,4,6 triiodobenzoate) is absorbed through the bladder from high concentration and capable thereby of yielding an excellent pyelogram

I^- is absorbed through the bladder from NaI in high concentration A weak pyelo-ureterogram can thus be obtained

Plain water, introduced into the bladder, is absorbed slowly

These data are all explicable by simple diffusion

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APPENDIX

Marucci, Shoemaker, Wase, Spraus, and Geyer (Proc Soc exp Biol Med, *87* 569-571, 1954) have studied absorption of iodine^{131}, phosphorus^{32}, and sodium^{24} through the normal canine bladder and through the experimental ileal bladder Radioactive assay showed only minimal absorption through the normal bladder but rapid absorption through the ileal bladder These studies, together with our observations on *net* absorption through the bladder, indicate that there is no significant exchange of ions across the normal bladder wall More work is necessary to corroborate or refute this supposition

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HERPES ZOSTER: A CAUSE OF ACUTE URINARY RETENTION

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Acute urinary retention is frequently associated with diseases or injuries of the spinal cord which involve the reflex centers of micturition or of the afferent or efferent nervous pathways to the bladder. These diseases may be a local involvement of the lumbosacral segment of the spinal cord by an infectious process such as transverse myelitis, by a vascular disease such as varicosities or thrombi of the blood vessels to the cord, by tumor or by a degenerative process, as found, for example, in multiple sclerosis. Systemic diseases, with local manifestations in the spinal cord, such as diabetes mellitus or pernicious anemia, may also cause acute urinary retention. The centers of micturition may further be implicated by edema or by exudation from disease processes involving neighboring structures in the spinal cord, such as occurs in poliomyelitis. The purpose of this paper is to present a neurological cause of acute urinary retention which, as far as can be ascertained, has not been previously described in American literature.

CASE REPORT

MBH Case No. 120-355, a 42-year-old white man was admitted to the hospital because of inability to void for 5 days. He stated that he had felt "under the weather" for about ten days before admission, but had no specific complaints until seven days prior to admission when several small lesions developed over his right buttock and thigh. He saw his local doctor who told him he had "shingles" and treated him with 250 mg. aureomycin 4 times a day. Five days prior to admission, the patient suddenly noted that he was having some difficulty passing his urine. He complained of dribbling of urine, but had no pain or burning on urination. Three days prior to admission, he was unable to void at all and was catheterized by his family doctor. When he failed to void on the following day he was advised to enter the hospital. The patient had never had any previous urinary difficulties.

The patient was well developed and well nourished. He wore an indwelling Foley catheter. Blood pressure 110/70, pulse 60, temperature 98.6, respirations 22. The skin of the right buttock and scrotum showed a number of papulovesicular lesions. The lesions varied from pinpoint to pea in size, bright red to dull red in color, dry or encrusted. The lesions were discrete and seemed to follow the course of the third and fourth sacral nerve. Examination of the head and neck revealed no abnormalities. Heart and lungs were normal. The abdomen was normal. The prostate was not enlarged, soft, smooth and moderately tender. The mucosa of the rectum was smooth. The rectal sphincter tone was normal. Neurological examination revealed hyperesthesia over the course of the herpetic lesions. There was good motor power in all extremities; deep tendon reflexes

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were equal and active in both legs and arms. No Babinski could be elicited. Cranial nerves were normal. There was not any other evidence of sensory changes other than those described over the area of the lesions.

Urinalysis: Specific gravity 1.022; alkaline reaction; albumin, sugar, acetone and diacetic acid, negative; microscopic examination showed occasional white cell. Urine culture negative. Hemoglobin 13.5 gm.; red blood cells 4,300,000; white blood cells 8,200; neutrophiles 52; lymphocytes 40; monocytes 8; nonprotein nitrogen 24; creatinine 1.8; blood sugar 77; serology negative. Roentgenograms of chest and abdomen were negative.

Shortly after admission, the patient's bladder was filled with fluid and the catheter removed. The patient, however, was unable to void. The catheter was reinserted, and he was placed on gravity drainage. At cystoscopy, the bladder mucosa was found to be smooth with minimal trabeculations at the bladder dome. The ureteral orifices were normal in size and position. There was a small median bar, but this was not considered sufficient to account for the complete urinary retention. *An attempt to have the patient void spontaneously at cystoscopy* was also unsuccessful. He was started on 250 mg. aureomycin 4 times a day, orally, and was given 5 mg. of urecholine subcutaneously 3 times a day. The patient was unable to void when the catheter was removed in 48 hours. Cystometric studies showed a bladder capacity of 675 cc with normal sensory responses to filling and normal intracystic pressure. On command to void, the patient had an intracystic pressure of 90 cm. of water. Sphincteric resistance was 21 cm. of water. The patient, however, was unable to void without a catheter. With sodium amytal narcosis, the patient was unable to void. On the eighth hospital day, the bladder was again filled with fluid. Four hours after the catheter was removed, *the patient voided spontaneously. He has not encountered* any further urinary difficulties since this time.

DISCUSSION

Herpes zoster is an acute inflammatory disease involving one or more dorsal root ganglia. In the acute stage the lesion consists of exudation of small round cells, extravasation of blood and destruction of ganglion cells and fibers. This may be followed by inflammatory changes in the corresponding segments of the spinal cord. In rare instances, paralysis of isolated muscle groups occurs, indicating involvement of the fibers or neurons of the anterior horn cells.

Micturition is essentially a reflex mechanism with its centers residing in the sacral segments, S2, 3 and 4 of the spinal cord. These centers occupy the length of about one lumbar vertebra. Furthermore, micturition is dependent upon co-ordinated detrusor contraction with almost simultaneous perineal relaxation. It may be readily seen that the edema and exudation accompanying herpes zoster of the sacral nerves could easily spread to the spinal cord to involve the entire reflex mechanism of micturition. As a result, the delicate co-ordinated mechanism of voiding is upset with resultant acute urinary retention.

Cystometric studies showed normal sensory bladder responses to filling. Intracystic pressure changes also followed a normal pattern, and on command to void, there was a definite increase in intracystic pressure sufficient, in normal cases, to initiate voiding. Sphincterometric study showed that only 21 cm. of water pressure was necessary in overcoming sphincteric resistance.

These two examinations were essentially normal and yet the patient remained in acute urinary retention for about 10 days. It is felt that, although these individual examinations were normal, urinary retention resulted from a failure of co-ordinating detrusor contraction with perineal relaxation. One of us (PHL), in studying vesical dysfunction in the paraplegic by electromyographic studies of the perineal floor, found that micturition occurred only when the perineal muscles relaxed while the detrusors contracted. In our patient this mechanism was temporarily lost, but was recovered when the disease process completely subsided.

In order to rule out hysteria as a basis of acute urinary retention, intravenous amytal was given. Under narcosis the patient failed to void.

Cystoscopic examination of the bladder was essentially normal and there was no evidence of any mechanical obstruction to the vesical neck.

SUMMARY

Acute urinary retention resulted from herpes zoster of sacral nerves three and four.

Explanation is offered of the mechanism of acute urinary retention.

We wish to thank Dr. Ray M. Bowles for his suggestions and criticisms in the preparation of this manuscript.

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CONGENITAL MEGALO-URETHRA

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Urethral diverticulum is an uncommon anomaly in male infants When detected its surgical management is usually not difficult, though not universally successful A very comprehensive consideration of this entire subject with an exhaustive review of the literature was made by Abeshouse in 1951 [1] The classification which he adopted does not by definition include the variety of abnormality to be discussed, yet one is unwilling to term this defect a urethrocele, a term used by Gausa Raspall in reporting a somewhat similar situation in the *Journal d'Urologie* [2] Urethrocele connotates a secondary acquired condition as contrasted to a condition present at birth The case to be reported is felt to represent a more rare variation of urethral diverticulum which might well be termed megalo-urethra The surgical technique used for correction of the abnormality was felt to be an interesting one which might be employed in other similar situations

CASE REPORT

An infant boy was admitted to the Urology Service of University Hospital at the age of 1 month The mother stated that an abnormally long penis had been noted at birth and with the first attempted voiding a tremendous dilatation of the shaft of the penis was noted by attendants The swelling was reduced by manual pressure on the distended portion with expression of what appeared to be normal urine The mother had been instructed on this method of decompression at the time of discharge from the hospital and had followed the instructions until the time of admission without intervening difficulties The infant was otherwise well

Examination disclosed a normal male infant except for a partially distended urinary bladder and a horrible phallic monstrosity The penis was C shaped, approximately 4 inches long and 3½ inches in circumference (fig 1, A) A partially phimotic foreskin was present and a pinpoint urethral meatus Decompression of the giant urethra was accomplished by external pressure on the shaft The urinary stream resulting was extremely small in caliber

Further studies showed the urine to be infected and the blood urea nitrogen was 35 mg per cent In light of these findings an emergency suprapubic cystotomy was performed the same afternoon for bladder decompression and a dorsal slit of the prepuce with a meatotomy The urethral meatus was gently dilated through 14F without difficulty Following this he improved rapidly and all indi-

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Read at annual meeting, North Central Section of American Urological Association, Detroit, Mich , October 9, 1954

* Present address 208 E Wisconsin Ave , Milwaukee, Wis

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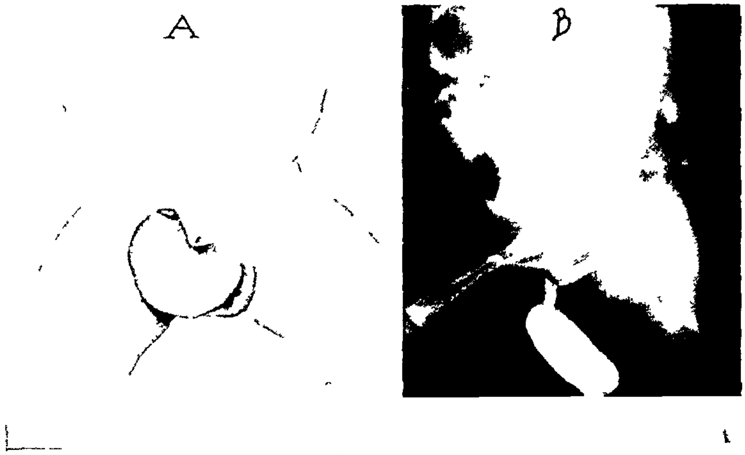

FIG. 1

cators of renal function returned to normal, including blood urea nitrogen, phenolsulfonphthalein excretion, and urea clearance. Excretory urograms were normal. A urethrocystogram demonstrated a tremendous saccular dilatation of the pendulous urethra from the penoscrotal angle to the meatus (fig. 1, *B*).

Surgical correction of the deformity was deferred until the age of 9 months, when the patient was re-admitted to the hospital, cystoscopy performed, and excellent visualization of the megalo-urethra was attained. The remainder of the urethra appeared normal and the external urethral sphincter seemed to be intact. The dilatation extended to within approximately two centimeters of the external sphincter.

SURGICAL TECHNIQUE

Following these studies surgical repair was deemed feasible and accomplished in this manner:

An encircling coronal incision was made in the foreskin leaving a mucosal cuff of approximately one-half centimeter in a fashion similar to that employed for circumcision (fig. 2, *A*). The skin and a portion of subcutaneous tissue of the entire penis were undermined, mobilized, and peeled back to the base of the penis just as one would roll back the sleeve on a coat (fig. 2, *B*). The penis was thus entirely denuded of skin, but the dilated urethra, covered now only by a thin segment of subcutaneous tissue, remained intact. The floor of the megalo-urethra was next incised vertically starting 4 mm. proximal to the external urethral meatus and extending to the urethral bulb (fig. 3, *A*). Urethral measurements at this point disclosed a width of 5½ cm., representing the circumference of the urethral lumen, and a length of 6½ cm. (fig. 3, *B*). The redundant flaps of lateral tissue were excised leaving a strip of normal urethra along the ventral surface measuring 16 mm. in width. The lateral margins of the remaining strip were approximated over a catheter with submucosal, interrupted sutures of fine catgut, and the catheter was removed (fig. 3, *B*). It was now obvious that the penile elongation was actually more apparent than real. The dorsal concave surface was only 2 inches long, because the corpora cavernosa and roof of the urethra

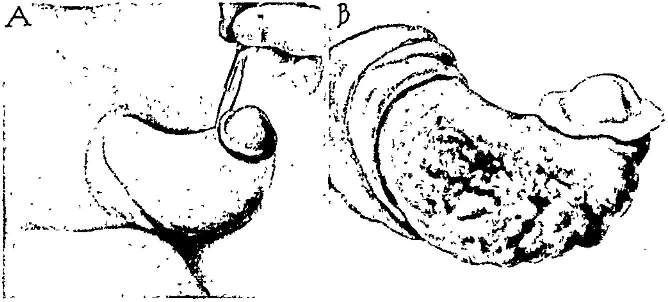

FIG. 2

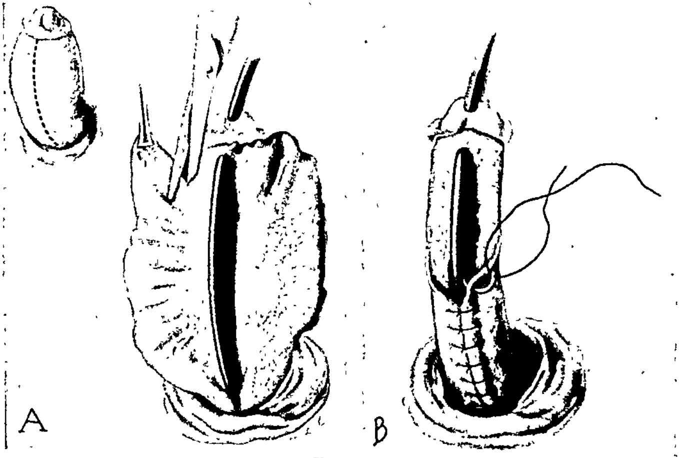

FIG. 3

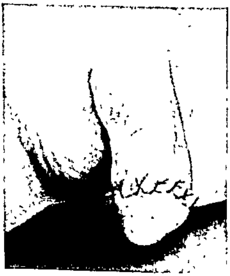

FIG. 4

had maintained their normal dimensions, whereas the convex ventral surface representing the distended urethra was over four inches in length. This discrepancy resulted in a redundant 1-inch of excessive skin, requiring removal as a napkin-ring cuff. The penile skin was rolled back down over the shaft of the penis and after simple excision of the excessive portion, the free margin was reapproximated to the mucosal cuff behind the corona, just as a circumcision is completed (fig. 4). The penis now had a normal appearance both as to length and circumference because the corpora cavernosa had not sustained any ill effects from the urethral deformity.

The child had an uneventful postoperative course and when the suprapubic cystotomy tube was clamped on the fourteenth postoperative day he voided a good stream of urine of normal caliber without distortion of the size of the shaft of the penis. A calibration of the newly formed urethra has since occurred after an elapsed period of 2 months for healing and the urethra accepts a 14F bougie readily.

DISCUSSION

This represents a unique form of a rare congenital anomaly likely secondary to obstruction at the urethral meatus occurring early in intrauterine life. It was the initial impression that this infant was destined to an existence with a horrible phallic deformity, and it was an extremely gratifying experience to find that a satisfactory correction could be attained. Formation of a normal sized penis was possible because the corpora cavernosa had been spared during the development and eventual formation of the megalo-urethra.

The single advantage to the technique, as described, lies in the prevention of urinary fistula. The greatest hazard to any such surgical repair is the occurrence of single or multiple fistulas, commonly due to two or more overlying suture lines, one of which is in the mucosa and one of which is in the skin. The method utilized avoids such a possibility by providing an intact integument to cover the suture repair line which would not conceivably break down so long as urinary diversion had been accomplished. Application of this principle of repair to other penile and urethral abnormalities of a similar nature would seem practical and worthwhile.

SUMMARY AND CONCLUSIONS

An unusual form of urethral abnormality has been reported which one might choose to term megalo-urethra in preference to urethrocele or urethral diverticulum. A somewhat different type of surgical repair of the defect has also been presented which it is believed will provide a greater degree of safety in avoiding the risk of fistula formation. The principle of repair should have a wide application to other anomalies of the penis and urethra.

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A SIMPLE TECHNIQUE FOR THE REPAIR OF PENOSCROTAL HYPOSPADIAS

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The accompanying drawings (fig. 1) demonstrate a simple technique for the repair of the penoscrotal type of hypospadias. It will be noted that by this procedure a urethra of large caliber is constructed, that no suture lines are overlaid, and that the constructed urethra is completed in one stage. It is apparent,

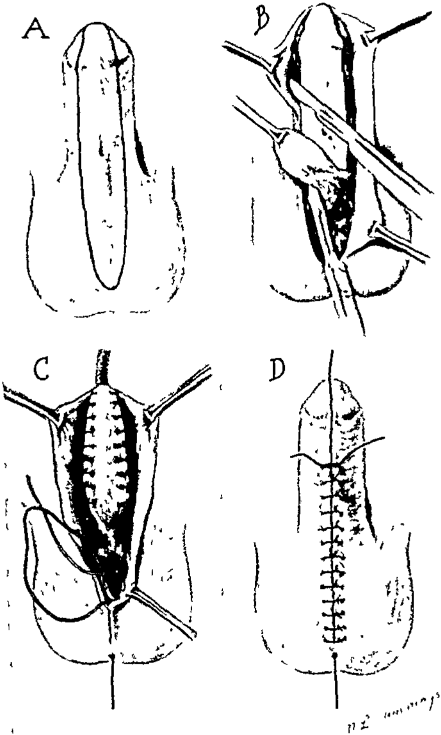

FIG. 1. *A*, note that planned scrotal raphe flap equals urethral deficit in breadth and length. *B*, flap is being developed as are scrotal and penile margins. *C*, scrotal flap sutured in place. *D*, margins of penile and scrotal incisions previously developed are approximated by subcuticular wire and interrupted chromic gut sutures.

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however, that a potentially hair-bearing surface is utilized in the construction of the floor of the urethra and that the new meatus is not anatomically perfect though approaching this desired result. In defense of the raphe scrotal flap it should be noted that proximal penile skin may not be free of hair and to this degree will complicate any repair not utilizing the scrotum. A cosmetically imperfect meatus is, of course, of little importance when weighed against a fistula free, functionally perfect, primary closure of a hypospadiac defect.

With this procedure it is assumed that the chordee has been corrected a reasonable time in the past and that the meatus is now located at or near the penoscrotal angle. These factors being complied with, the child is placed on cystostomy drainage and the urethral constructive operation carried out as illustrated. This consists of swinging a raphe scrotal flap of correct width and length to conform with the entire ventral surface of the penis, its suturing with fine chromic gut to the margins of its counterpart on the ventral surface of the penis thus constructing the urethra, and closure through the approximation of laterally mobilized penile skin in continuity with the skin of the scrotal surgical defect by means of a subcuticular wire suture running from the distal end of the scrotal incision to the end of the penis. The skin margins are united by interrupted sutures of fine chromic. Any tension resulting in approximating the penile skin over the new urethra is released by means of a longitudinal incision on the dorsum of penis which may be left open or closed transversely.

It should be added that in those instances where the hypospadic meatus is small a segment of margin is excised and transverse closure made in such a way that a larger meatus is attained.

Postoperatively the subcutaneous wire suture is removed on the seventh day and the cystostomy tube at the end of 2 weeks.

CONCLUSION

A technique for repair of penoscrotal hypospadias is described whereby a fistula-free primary closure is attained.

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ADENOMATOID TUMORS OF THE EPIDIDYMIS

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Primary tumors of the epididymis are rare Until September 1949 there were reports of 134 cases in the literature of which 74 per cent were benign and 26 per cent malignant[1] The most common benign tumor of the epididymis is the so called "adenomatoid" tumor which accounts for approximately 70 per cent of the benign tumors A total of 88 adenomatoid tumors had been reported up to September 1949[1] Since then we have been able to find reports of ten more cases[2, 3, 4, 5, 6, 7, 8] We wish to report two additional cases

Terminology used to describe these tumors has been variable until recent years Since the first tumor of this type was reported in 1916 by Sakaguchi[9] as an adenomyoma they have been described by various authors as adenoma, adenofibromyoma, mixed tumor, lymphangioma, mesothelioma, adenocarcinoma and even lymphangiosarcoma[8] The tissue of origin of these tumors cannot be definitely determined There are several discussions on this matter in the literature[10, 11, 12] However, since this point does not appear to be of any practical importance, the term adenomatoid, as suggested by Golden and Ash,[11] seems most suitable in view of the microscopic appearance of this tumor

Adenomatoid tumors are always benign, no case of local recurrence, metastasis, or death due to these tumors having ever been reported Treatment thus consists entirely of local excision

The gross appearance typically is that of a well encapsulated, globular, smooth tumor It is usually firm, whitish, with a diameter of 1 to 5 cm Cross section reveals homogeneous greyish white, pinkish or yellowish tissue which often presents a whorled appearance

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An adenomatoid tumor is most commonly found attached to the lower pole of the epididymis. The lower pole is involved four times as often as the upper pole. The left epididymis is affected twice as often as the right. No multiple or bilateral tumors have been reported. In addition to the epididymis, adenomatoid tumors may be found attached to the uterine tubes, uterus, ovary, tunics of the testicle or spermatic cord. These tumors, of course, do not transilluminate and this is helpful in differentiating cyst of the epididymis.

Most commonly encountered in the third and fourth decades of life, these neoplasms have been reported in the elderly and in a newborn.[3] Usually the tumor is first noticed as a symptomless nodule in the scrotum, almost always painless and nontender. In only five previously reported cases had pain been prominent and in only three had pain been the presenting symptom. It will be seen later that one of our new cases presented with pain.

Microscopically numerous gland-like spaces are seen lying in a moderate or scanty amount of fibrous connective tissue stroma. The gland-like spaces are of varying sizes and shapes and are seen to be lined with cells which vary from flat endothelial-like cells to low columnar. The gland-like spaces are usually empty but occasionally desquamated cells may be seen. Red blood cells are never seen in these spaces. The cells lining these spaces contain a small to moderate amount of finely granular acidophilic cytoplasm. Brush borders have been described using Mallory's phosphotungstic-acid stain.[1] The nuclei of these lining cells are round or oval, stain deeply and are often centrally placed. However, often many of the cells are vacuolated with a signet ring appearance. Glomeruloid or glomerulus-like structures have been described in some cases. These consist of projections of the walls into the gland-like spaces.

The stroma of fibrous connective tissue may at times contain hyalinized areas. Sometimes smooth muscle bundles may be seen. Lymphocytes are often seen lying in the stroma and sometimes focal collections of these cells are seen resembling lymph follicles (fig. 1, *B*). Polymorphonuclear leukocytes and necrosis have been described in only 1 case[6] and were probably due to secondary changes in the tumor.

CASE REPORTS

Case 1. A 57-year old, white, married man complained to his family physician of moderately severe backache (dorsal and upper lumbar areas) of several weeks' duration. His physician, in the course of general physical examination, found a "stony hard nodule" in the right epididymis which was not tender. The patient had been aware of the nodule for "several weeks" but it had not bothered him in any way. Subsequent examination revealed the nodule to be attached to the upper pole of the right epididymis. It was spherical in shape and had a diameter of 1.5 centimeters. X-rays of the spine showed spondylolisthesis with forward displacement of the body of L4 on L5. There was also osteoarthritis of the dorsal and lumbar vertebrae and calcification of the abdominal aorta. Conservative management relieved his backache and the nodule was removed from the upper pole of the epididymis. Gross appearance of the tumor was that of a well encap-

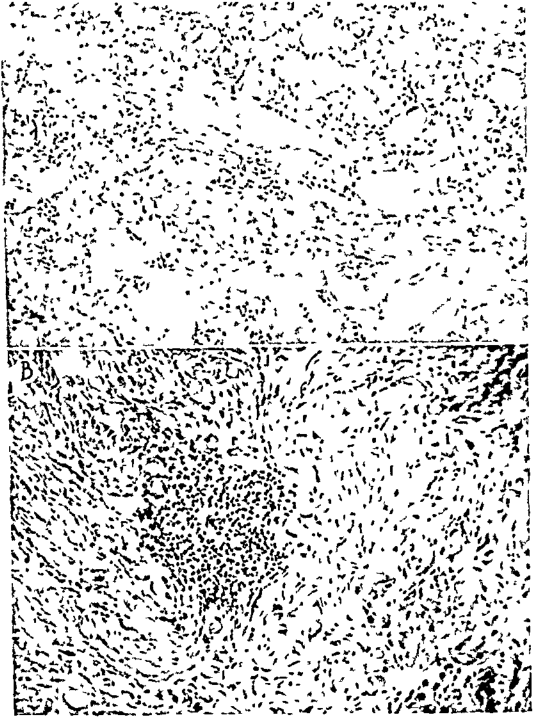

Fig. 1. *A*, case 1. Note numerous gland-like spaces lined by flattened, endothelial-like cells and scanty fibrous stroma with a diffuse sprinkling of lymphocytes ×160.

B, case 2 Note more abundant stroma, vacuolated cells, and focal collection of lymphocytes in stroma. ×160

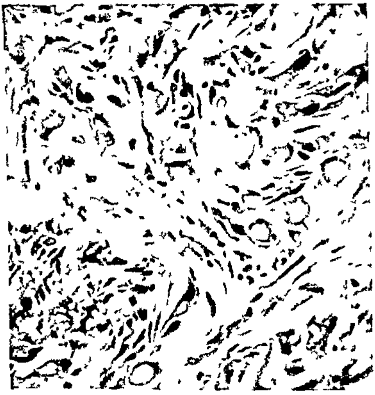

Fig 2 Case 2 Higher power to show more abundant acidophilic cytoplasm of cells lining gland like spaces Note vacuolated cells ×620

sulated spherical nodule measuring 1.5 cm. in diameter. Cut surface revealed homogeneous white tissue. Microscopically (fig. 1, *A*) numerous gland-like spaces were seen lying in an extremely scanty stroma of fibrous connective tissue. The cells lining the spaces were very much flattened and drawn out, closely resembling endothelial cells. The cytoplasm was acidophilic and the nuclei round and well stained. The gland-like spaces were empty. There were a fair number of lymphocytes throughout the stroma and several focal collections of lymphocytes.

This tumor was removed 8 years ago (1946) and to date there has been no recurrence of tumor or symptoms.

Case 2. A 29-year old, white, married man complained of dull, aching pain in the left testicle of 6 months' duration. The pain originated in a "little nubbin" attached to the left testicle and radiated upwards into the left groin. The pain was almost constant in character but increased in severity after heavy work. In the weeks just prior to examination the pain had become worse and had interfered with sleep. There was no past history of venereal disease, operations or serious illnesses.

He had no other genito-urinary symptoms and had no other complaints. Physical examination revealed a firm, tender nodule, 1.5 cm. in diameter and spherical in shape, firmly attached to the upper pole of the left epididymis. The remainder of the physical examination was negative.

Urinalysis was negative; hemogram was normal and the serological tests for syphilis were negative.

An incision was made through all scrotal coats down to the tumor mass which was firmly attached to the epididymis. By sharp dissection the tumor was removed. Four days later the entire left cord and testicle were removed in view of a pathological report of sarcoma.

The gross and microscopic appearances of this tumor were almost identical to that in case 1, except that microscopically the stroma in case 2 was much more abundant and the cells lining the gland-like spaces contained considerably more cytoplasm (figs. 1, *B* and 2) and vacuolated cells were very numerous.

The patient had no recurrence when last seen 5 years postoperatively.

SUMMARY

A brief review of the clinical and pathological aspects of adenomatoid tumors of the genital tract is presented.

Two additional cases are reported bringing the total to 100 cases.

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A STUDY OF DRAINAGE TUBES AFTER SUPRAPUBIC PROSTATECTOMY

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The purpose of this paper is to report the results of our efforts to find out why such a high incidence of postoperative bladder neck contractures follows suprapubic prostatectomy

This study was prompted by a report that was given some 2 years ago from one of the urological services of Cook County Hospital At that time a large incidence of postoperative contractures of the vesical neck was reported following suprapubic prostatectomy There was no comparable incidence of postoperative bladder neck contractures on the other urological service of the same hospital

The technique of suprapubic prostatectomy has been fairly well standardized A vertical suprapubic midline incision is made through the skin, fat and fascia The recti muscles are separated and the prevesical peritoneal apron is reflected cephalad off the bladder The bladder is always filled with sterile water before the operation The bladder is emptied by means of a trochar The trochar opening is enlarged to medium size, up and down The anterior prostatic commissure is broken through with the right index finger to find a line of cleavage Enucleation is greatly aided and facilitated by the index finger of the left hand in the rectum Bleeding is controlled by moist, hot, laparotomy pads which are placed into the prostatic cavity When bleeding has been controlled, the internal vesical orifice is freed of tags If the interureteric ridge is obstructive, a turbinate punch is used to remove this obstructing tissue It happens that it was not necessary to do this in any of the patients of this study A 22 or 24F bag catheter is passed through the urethra on a mandarin and the bag is inflated enough so that when it is pulled down it compresses the prostatic cavity to control hemorrhage The bladder is closed around a dePezzer catheter A soft rubber drain is placed in the space of Retzius and the wound closed in layers by interrupted catgut and silkworm gut

After a review of the histories of some of the patients who had postoperative bladder neck contractures following suprapubic prostatectomy, it was noted that the suprapubic drainage tube was removed in 48 to 72 hours and the urethral bag catheter was left in situ 5 to 10 days to permit the suprapubic wound to heal well The other urological service removed the urethral bag catheter in 24 to 48 hours and left the suprapubic cystotomy tube in place 8 to 10 days When the cystotomy tube was removed, the patient was instructed to stand up to void every hour during the day and he was awakened every 2 hours to do the same at night If he voided increasing larger amounts, the cystotomy wound healed soon and the belly wall became dry If he was unable to void, an indwelling urethral catheter was placed from 48 to 72 hours

So, it was decided to use each method of managing the drainage tubes on the

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Read at annual meeting, North Central Section of American Urological Association, Detroit, Mich , October 7-9, 1954

TABLE 1

Case No.	Urethral Cath. No. day	Cystotomy tube. No. days	Urethritis	Contracture	Subjective Complaints
1	30	3		Moderate	None
2	14	3		Moderate	Nocturia, 5 times
3	26	3		Moderate	None
4	6	3	Present	Marked	Cloudy urine
5	41	3		Marked	Nocturia, 4 times
6	12	3		Moderate	None
7	10	2		Moderate	Nocturia, 2 times
8	18	3		Moderate	Cloudy urine
9	8	3		Marked	Nocturia, 4 times
10	3	8		Slight	None
11	13	12		Slight	None
12	3	9		Slight	None
13	13	18		Moderate	None
14	2	9	Present	Moderate	Cloudy urine
15	37	10		Marked	Cloudy urine
16	3	12	Present	Marked	None
17	4	10		Slight	None
18	3	7		Slight	None

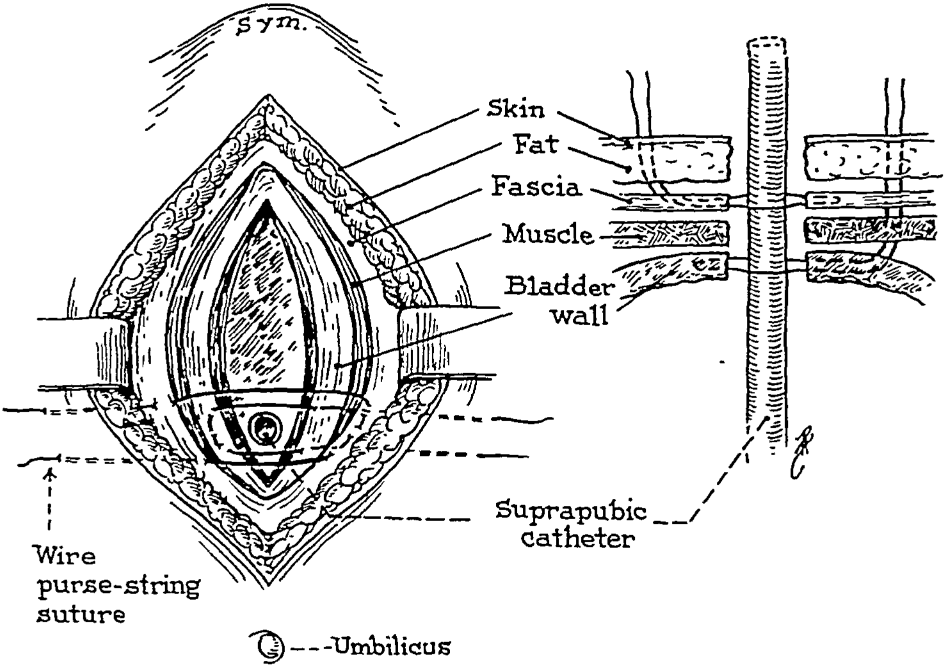

FIG. 1

same number of patients and examine them every week after their dismissal from the hospital. At the end of 3 to 6 months an observation cystoscopy with a fore-oblique panendoscope was done, by an experienced cystoscopist, to estimate the degree of vesical neck contracture and scarring.

The patients, 25 in number, were dismissed from Cook County Hospital, with instructions to return to the outpatient urological clinic for their postoperative care. Only 18 patients of the 25 complied with our request. Cystoscopy was performed with a foroblique panendoscope in order to observe properly the internal vesical orifice and prostatic bed. An effort was made to determine whether there was slight, moderate, marked or no contracture of the vesical neck. The cystoscopist did not know how the drainage tubes had been handled in each instance.

Judging from table 1, it would seem that there is a direct correlation between the severity of the postoperative vesical neck contracture and the length of time which the urethral catheter was allowed to remain in the urethra. Those patients who were permitted to retain a urethral catheter for any period *longer* than 3 days were very likely to have a slight to marked postoperative bladder neck contracture. On the other hand, those patients whose indwelling urethral catheters were removed within 3 days or less had a *low* incidence of postoperative bladder neck contracture.

It is also apparent that in every patient who had purulent urethritis as a result of the indwelling catheter marked postoperative bladder neck contracture was certain to develop. The most marked contractures were seen in those patients who had worn their urethral catheters over long periods of time.

It is interesting to note that about one-half of the patients, with a postoperative bladder neck contracture, had *no* subjective complaints. The rest had urinary complaints, the severity of which depended upon the degree of contracture.

It would seem from this study that the presence of a foreign body in the urethra invites infection and results in varying degrees of postoperative bladder neck scarring after suprapubic prostatectomy.

We have, therefore, initiated the practice of placing a wire pursestring suture to hold the cystotomy tube in place and to appose fascial layers of the suprapubic wound (fig. 1). The urethral bag catheter is removed in 48 hours. The cystotomy tube is removed in 4 or 5 days, after which the wire pursestring stitches in the bladder and fascia are drawn tight to occlude the cystotomy opening and obtain a dry wound. This converts the incision to a wound which heals by primary intention and permits the removal of all drainage tubes at an early date. Thus far, no postoperative bladder neck contractures have occurred in patients on whom we have used this method of managing the drainage tubes. This method of closure will also help to prevent the extended hospital convalescence due to persistent suprapubic fistulas.

SUMMARY

A preliminary study indicates that a relationship exists between the length of time that an indwelling urethral catheter is in place and the incidence of contractural scars of the internal vesical orifice after suprapubic prostatectomy.

A modified method of early closure of the suprapubic fistula to permit early removal of the urethral catheter after suprapubic prostatectomy is described.

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STUDIES ON FLUID ABSORPTION DURING TRANSURETHRAL PROSTATIC RESECTION

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Since the appearance in 1947 of several articles[1, 2, 3] discussing the now well known syndrome of intravascular hemolysis during transurethral prostatic resection, it has been generally assumed that a certain amount of the irrigating fluid passes directly into the prostatic veins. This has been demonstrated to everyone's satisfaction and since it was considered inevitable, efforts were made to prevent hemolysis by the use of isotonic irrigating solutions.

The first solution tried was glucose in 5 per cent concentration.[4] This satisfactorily prevented intravascular hemolysis in a controlled series but was found to be unpleasant to use and also obscured vision somewhat. The pros and cons of the use of glucose are discussed by several authors[5, 6] and we believe the general opinion now is that other solutions are probably better. Urea was tried in varying concentrations[7, 8, 9] and found by some to be satisfactory while others thought it was in no way superior to distilled water. Nesbit was first to suggest the use of glycine[9, 10, 11] and later mannitol,[12] both of which are satisfactory in every respect except that the complete lack of hemolysis obscures vision somewhat. The authors, having had no experience with distilled water in transurethral resection, are in no position to make a comparison and find the visibility adequate with glycine.

The only recorded quantitative estimate of the amount of fluid absorbed is that

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of Landsteiner and Finch[3] who "tagged" the irrigating solution with salicylic acid and found, by postoperative blood levels, that about one liter of fluid had entered the vascular system[3] Nesbit determined by postoperative blood levels that glucose also entered the circulation but made no attempt to calculate the amount Since glucose is readily metabolized, accurate determination would be difficult On the other hand Ebert was unable to find any significant elevation of blood urea following resections where the irrigating solutions contained 1 8 per cent urea[7] This may have been due to rapid destruction of the urea by the liver In view of these findings it seems probable that a significant amount of fluid would be absorbed during any reasonably complete resection Since many patients are subjected to this form of prostatectomy solely because their cardiovascular status is precarious, the rapid accumulation of this much fluid might well be disastrous Our object in this study was to determine as accurately as possible the amount of fluid absorbed in relation to the amount of tissue removed and the time spent in resection

Glycine solution 2 5 per cent (recently 1 25 per cent) is used in this clinic exclusively and has been satisfactory in every respect There has been no morbidity or mortality associated with either hemoglobinemia or oliguria One post transurethral resection fatality did occur, however, and consideration of that case prompted this investigation

METHODS

A simple and logical method would be to determine the postoperative blood levels of glycine but this was unsatisfactory because it, also, is rapidly metabolized and because serum level determinations of glycine or of total amino acids are very difficult Fortunately we had available an accurate bed scale and each patient was carefully weighed immediately before and after surgery Allowance was made in each case for intravenous fluids given during the procedure, the amount of tissue removed and the blood loss Blood loss determinations were made in each case and will be mentioned later Controls in this instance were two patients who had transurethral fulguration of bladder tumors without prostatic resection These normally short procedures were deliberately lengthened so that the bladder was irrigated about the same length of time required for a prostatic resection Neither case showed significant weight gain

MATERIAL

The patients used were routine admissions to this hospital and the majority of the resections were performed by the resident staff A few were performed by the consulting and attending staff in order that the series would more nearly conform to work done by practicing urologists The cases were taken consecutively in so far as possible, and, in line with the usual procedure, the larger glands were removed by open surgery Postoperative morbidity in this series was confined to epididymitis in 2 cases, bleeding in one case which required readmission but not transfusion, and another case where readmission was not necessary There were no fatalities

RESULTS

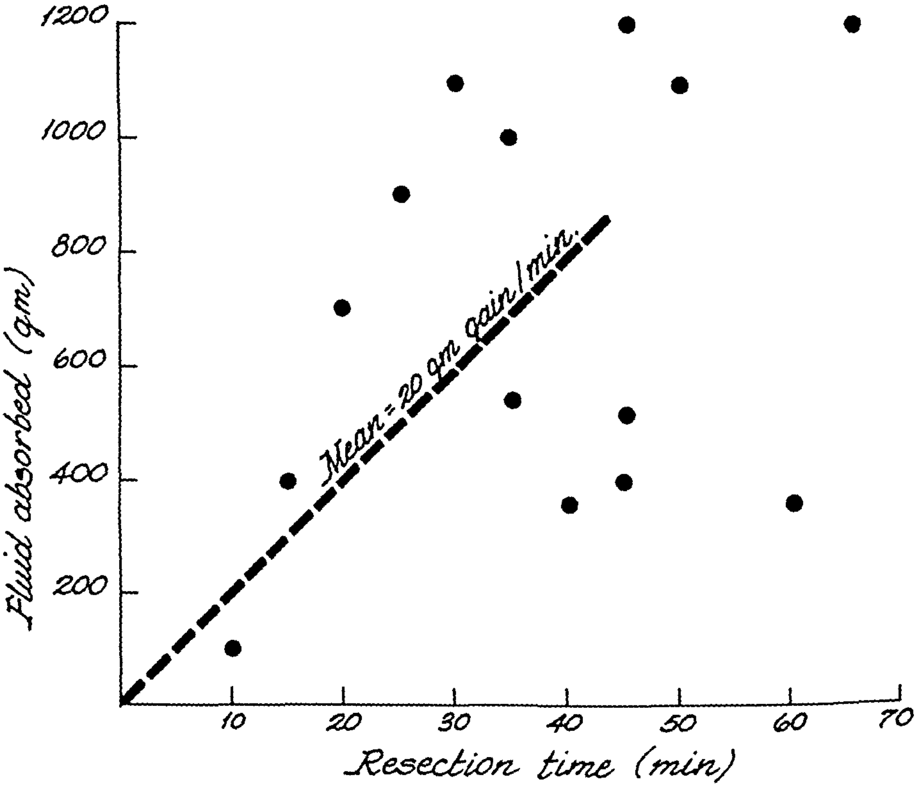
Sixteen patients had transurethral resection of a contracted bladder neck and/or prostatic adenoma. The tissue removed varied from 5 gm. to 32 gm.; resection time from a few minutes to 1 hour and the net weight gain from 100 gm. to 1250 gm. One case showed no change and was assumed to be an error in technique at some point.

Figure 1 is a graph, plotting the amount of fluid absorbed (as weight gain) against the resection time. The correlation here was fairly good and most of the cases fell within a range of 10 to 30 cc of fluid absorbed per minute of operating time. The mean was 20 cc per minute and is indicated on the graph by the dotted line.

Figure 2 similarly plots fluid absorbed against the amount of tissue removed. Here the correlation is poor, varying from 6 to 120 cc of fluid absorbed per gram of tissue removed. The mean is 61 gm. of weight gain per gram of tissue removed.

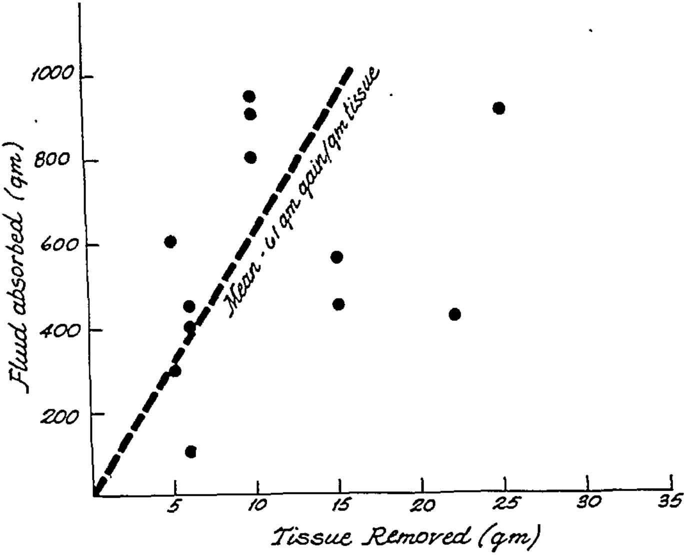
Figure 3 relates fluid absorption to blood loss. The variation here is from 5 to 38 cc of absorbed fluid per cubic centimeters of blood lost, and the mean is 9.2 cc of absorption per cubic centimeters of blood lost.

Statistical analysis of a series this small is fraught with danger and perhaps



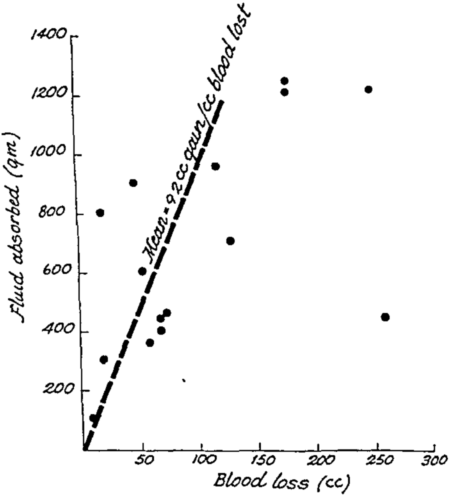
Average fluid gained compared to resection time = 20 gm fluid/min. varied from 7 gm to 32 gm gained per minute

FIG. 1



Average fluid gained compared to tissue removed = 61 gm fluid/gm tissue resected varied from 10 gm to 120 gm per gm tissue resected

FIG. 2



Average fluid gained compared to blood lost = 9 2 gm fluid per cc blood lost · varied from 16 gm to 38 gm gained per cc blood lost

FIG. 3

the preceding deductions somewhat presumptuous. We are convinced, however, that fluid absorption does occur during transurethral prostatic resection and that it occurs in the order of magnitude indicated by the previous figures.

BLOOD LOSS

In order to determine correctly the fluid absorbed it is necessary to know the blood loss, as this must be added to the observed weight gain in order to arrive at a true figure. This was determined simply, by collecting the wash water, measuring and sending an aliquot to the laboratory where a red cell count and a hemoglobin determination were done. By use of the following formulas the loss was calculated.

Hemoglobin method:

$$\text{Blood lost (cc)} = \frac{\text{Hgb. in wash water (gm. \%)} \times \text{vol. of wash water (cc)}}{\text{Patient's hgb. (gm. \%)}}$$

Red Blood Cell Method:

$$\text{Blood lost (cc)} = \frac{\text{RBC in wash water (per mm.}^3\text{)} \times \text{vol. of wash water (cc)}}{\text{Patient's RBC (per mm.}^3\text{)}}$$

These formulas were checked by adding 5, 50, and 100 cc of blood respectively to 8000 cc of glycine solution. These dilutions were calculated in the above manner and the hemoglobin method found to check with not more than 6 per cent error in any case. In all three instances the error was greater, rather than less, than the amount of blood used. The red cell method did not check nearly so well and was consistently lower. However, the results were always in the same order of magnitude and served as a useful check on the hemoglobin determination. We felt the discrepancy was explained by the following:

1) Hemolysis due to the cutting and coagulating current.
2) Hemolysis due to physical trauma to the cells during collection and mixing.
3) Varying degrees of clumping and rouleaux formation which made accurate counting impossible.

This may not be as accurate as other methods[13] but is sufficiently accurate for this purpose. Being quick, easy and inexpensive, it lends itself for use by any resectionist who wishes to check his own operative blood losses. As many men apparently still use distilled water,[11] their blood losses could also be measured by the hemoglobin method.

This institution uses the alkaline hematin method of hemoglobin determination, utilizing a permanent standard prepared by Dr. J. H. Gast of the Department of Biochemistry, Baylor University College of Medicine. Instead of the usual 20 cmm. of blood, 1 cc of wash water was diluted to 5 cc with 0.1 N sodium hydroxide and read against the standard in the usual manner. A suitable correction was then made for the difference in volume of the specimen. When necessary, more or less than 1 cc of the wash water may be used. These calculations apply equally well to the acid hematin method.

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[13] Nesbit, R. M. and Conger, K. B.: Studies on blood loss during transurethral prostatic resection. J. Urol., 46: 713, 1941.

CASE REPORT

Mr. C. W., a 67 year old white man, was admitted in December 1953 for recurrent congestive failure. In the preceding 7 years he had had 15 admissions with the same diagnosis, and treatment had included digitalis, diuretics, bed rest and low salt diet.

Physical examination: Blood pressure 158/94, pulse 84, respirations 24, temperature 99.6 degrees. The cervical veins were engorged and there were moist rales at both lung bases. The heart was enlarged to the left and a blowing systolic murmur was present at the base. The liver was enlarged and tender and there was edema up to the thighs, including the scrotum. The venous pressure was elevated and circulation time prolonged. An electrocardiogram showed left axis deviation and myocardial insufficiency. Admission urine showed many white blood cells and bacteria, and shortly after admission bilateral flank pain developed. Urine culture grew Pseudomonas aeruginosa and gamma streptococci. The usual cardiac measures were instituted but the patient responded more slowly than he had on previous admissions. A diagnosis of congestive heart failure due to arteriosclerotic and hypertensive cardiovascular disease, precipitated by pyelonephritis, was made.

Blood chemistry studies at that time were: blood urea nitrogen 47 mg. per cent; CO_2 28 mEq/L; chlorides 87 mEq/L; sodium 121 mEq/L; potassium 3.3 mEq/L; hemoglobin 10 gm. per cent; red blood cells 3,200,000. On the basis of these results a more liberal salt allowance was ordered. Cystoscopy showed a grade 2 trilobed prostatic enlargement. Marked obstruction was indicated by trabeculation, cellules and hypertrophy of the interureteric ridge. A Foley catheter was left inlying. Electrolyte chemistries were repeated and were within normal limits. The pyelonephritis responded slowly to treatment and after a delay of one month a transurethral prostatic resection was performed under spinal anesthesia. Early in the procedure the patient became restless and was quieted by a small amount of intravenous pentothal sodium. Toward the end the patient suddenly became cyanotic and the blood pressure aburptly arose to 180/110. The procedure was discontinued and oxygen was given. Except for coma, cyanosis and hypertension, examination was not remarkable. Operative time was 50 minutes and 13 gm. of tissue were removed.

The serum sodium was depressed to 124 mEq/L; chlorides 94 mEq/L; CO_2 15 mEq/L and potassium 3.4 mEq/L. The patient was severely oliguric for 20 hours (150 cc output) postoperatively but when 150 cc of 5 per cent sodium chloride was given intravenously he excreted 450 cc of urine in the next 8 hours. During this period the coma lifted dramatically, and the patient began to eat and take oral fluids. No other intravenous therapy was required. The blood urea nitrogen continued to rise and reached 121 mg. per cent on the third postoperative day and then fell to normal on the seventh day.

Having been impressed previously with the fact that fluid absorption did occur and that it might conceivably cause cardiac embarrassment in borderline cases, the patient received a mercurial diuretic the day before surgery in order that he might be in the best possible condition. This resulted in a profuse diuresis.

DISCUSSION

The case report mentioned earlier is one of a small series of cases representing about ½ of 1 per cent of some 1500 transurethral resections. These cases will be discussed in greater detail in a later report. Briefly, however, this atypical reaction occurred in the poorer risk patients, most of whom had cardiac disease and long histories of salt depletion due to low salt diet.

Almost invariably the patient became "restless" and was further sedated during the procedure. This was followed by abrupt onset of cyanosis, coma and hypertension. There was no unusual operative experience; the resections were neither unusually prolonged, bloody nor difficult. In most cases the coma persisted and the patient died without regaining consciousness. In others, spontaneous recovery occurred after a period of marked oliguria. We feel that intravascular hemolysis was not a factor because glycine solution was used and because there was no abnormal hemoglobinemia.

It is our belief that the underlying pathological process is a low serum sodium level, usually a result of cardiac therapy. This low level is reduced beyond the critical point by the sudden acquisition of a large amount of water which results in further dilution. The actual process is not clear but may be cerebral edema and increased intracranial pressure caused by the extreme hypotonicity of the extracellular fluid which loses water to the cells. The general debility of the patient is, of course, a contributing factor.

Again referring to the case reported, a proven low serum sodium was corrected to normal by a regular diet, only to be lowered on the day prior to surgery by the mercurial diuresis. This patient was not weighed before and after operation but the very low serum sodium obtained on the first postoperative day points to the underlying pathologic physiology. The dramatic response after the intravenous injection of 130 mEq of 5 per cent NaCl is further confirmation.

If we may apply the data derived from this study, the patient may be assumed to have absorbed 1000 cc (plus or minus 200 to 300 cc) of fluid. Obviously no person with cardiac decompensation would normally receive this sort of intravenous insult, which in addition to overloading the heart, also precipitated a critical hyponatremia. This syndrome is discussed in detail by Moyer,[14] to whom we are indebted for first calling our attention to the possibility that it might apply here.

If, in the future, we assume that an increased cardiovascular load will result from significant fluid absorption during a transurethral prostatic resection, allowance can be made for it. Or—and this is carrying the presented facts to a logical conclusion—we could check the serum electrolytes on any patient with a history of chronic salt depletion. Low values may be corrected prior to surgery and an immediate postoperative serum sodium determination would be a guide to future therapy.

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[14] Moyer, C. A.: Fluid Balance. Chicago: Yearbook Publishers, 1953.

Transurethral resection of the prostate, by all standards, is an excellent procedure with low mortality and morbidity If these facts of fluid absorption and hemodilution are kept in mind, it is possible that a slight, but significant, further reduction in morbidity and mortality may result

SUMMARY

Several cases of transurethral prostatic resection have been studied to determine the amount of fluid absorbed during the procedure This was determined by the amount of weight gained by the patient during the operation and was found to vary from 100 cc to 1250 cc Further evaluation was made by comparison of the amount of fluid absorbed with the time of resection, amount of tissue removed and the blood loss The resection time gave the best correlation with the weight gain, the average of all cases being 20 cc of fluid absorbed per minute of operating time

An illustrative case was presented The patient was an elderly man with chronic heart failure who experienced coma, cyanosis and hypertension during a transurethral resection This was felt to be due to pre existing hyponatremia aggravated by rapid hemodilution This responded rapidly to administration of intravenous 5 per cent NaCl The pathologic physiology is discussed as well as suggestions for prevention and treatment

We are indebted to Dr Ferrin B Morland and his laboratory for their kind co operation in doing the many examinations required for the blood loss determinations

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[14] Moyer, C. A.: Fluid Balance. Chicago: Yearbook Publishers, 1953.

TABLE 1

Patient	Age	Prostatic Tissue Resected (grams)	Duration Resection (minutes)	Quantity Irrigating Fluid (liters)	Estimated Blood Loss (mls)	Parenteral Fluids (ml): Blood	Parenteral Fluids (ml): 5% Glucose/water	Parenteral Fluids (ml): Isotonic saline
Operated Patients								
O_1	71	15	70	19	200	380	150	550
O_2	80	20	80	28	150	100	800	200
O_3	70	10	60	10	110	—	300	200
O_4	86	14	60	20	280	500	120	300
O_5	70	23	90	17	320	500	300	200
O_6	77	18	75	21	140	—	800	200
O_7	69	11	100	25	200	—	750	150
Control Patients								
C_1	73	—	—	—	—	—	—	—
C_2	74	—	—	—	—	—	—	—
C_3	70	—	—	—	—	—	—	—
C_4	58	—	—	—	—	—	—	—

and Gregerson,[4] extracellular fluid space was measured by the sodium thiosulfate method of Cardozo and Edelman [5] Plasma protein concentration was ascertained by method of Weichselbaum [6] Total blood volume and red blood cell volume were derived from the hematocrit and plasma volume Sodium and potassium concentrations of both serum and tissues were determined by the use of an internal standard flame photometer Chloride estimations were derived according to the method of Logans [7]

RESULTS

The ages of all patients and the essential details of the operations are recorded in table 1 The fluid volume and electrolyte data have been divided into four groups in order to simplify analysis

In the first group (represented by table 2) are listed the preoperative and postoperative serum sodium, potassium, chloride, protein, hematocrit and hemoglobin values of the operated patients as well as the "pre-rest" and "post rest" determinations of the control patients It will be observed that the postoperative results are essentially unchanged from the preoperative values, the control determinations indicate that the variations observed are within the limits of laboratory error

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[4] Noble, R P and Gregerson, M I Blood volume in clinical shock I Mixing time and disappearance rate of T 1824 in normal subjects and in patients in shock Determination of plasma volume in man from 10 minute sample J Clin Invest, 25 158, 1946

[5] Cardozo R H and Edelman, I S The volume of distribution of sodium thiosulfate as a measure of the extracellular fluid space J Clin Investig, 31 280–290 1952

[6] Weichselbaum, T E Accurate and rapid method for determination of proteins in small amounts of blood serum and plasma J Clin Path, 16 Tech Sect 10 40–49 1946

[7] Logan M A Composition of cartilage, bone, dentin, and enamel J Biol Chem, 110 375, 1935

TABLE 2

Patient		Serum Sodium mM/L	Serum Potassium mM/L	Serum Chloride mM/L	Serum Protein gm. %	Hematocrit vol. %	Hemoglobin gm. %
Operated Patients							
O_1	Pre op.	143.6	4.8	103.6	6.6	40.2	14.7
	Post op.	132.0	4.4	95.9	6.7	42.7	14.4
O_2	Pre op.	143.7	4.0	103.5	6.4	45.7	15.7
	Post op.	143.6	3.6	96.7	5.7	41.5	14.5
O_3	Pre op.	143.0	5.5	106.5	7.3	36.8	12.5
	Post op.	143.7	5.0	105.3	6.8	33.2	12.1
O_4	Pre op.	146.2	4.4	110.5	5.8	37.2	13.4
	Post op.	142.5	4.7	109.5	5.7	36.6	16.8
O_5	Pre op.	139.8	3.9	110.1	5.5	41.7	19.9
	Post op.	146.5	3.1	101.8	6.0	42.2	17.5
O_6	Pre op.	148.5	4.4	105.0	6.4	42.7	16.6
	Post op.	141.8	4.6	101.3	6.6	45.1	17.0
O_7	Pre op.	138.8	4.5	103.8	6.0	43.6	16.1
	Post op.	138.7	4.5	96.5	4.6	39.8	14.5
Control Patients							
C_1	Pre rest	145.0	4.7	105.3	6.2	40.8	14.5
	Post rest	146.0	4.3	107.3	6.3	38.4	14.3
C_2	Pre rest	148.6	2.6	93.5	6.7	42.4	13.6
	Post rest	150.5	2.7	95.8	7.0	39.9	13.0
C_3	Pre rest	144.2	4.5	102.3	6.5	43.7	15.3
	Post rest	145.6	4.6	102.3	6.5	42.1	14.7
C_4	Pre rest	139.7	4.5	98.8	7.6	41.7	16.1
	Post rest	144.2	3.8	99.3	7.7	40.5	14.3

TABLE 3

Patient		Serum Volumes (ml.)	Calculated Change	Blood Volumes	Calculated Change
Operated Patients					
O_1	Pre op.	2994	−191	4705	−126
	Post op.	2803		4579	
O_2	Pre op.	2661		4565	
	Post op.	—		—	
O_3	Pre op.	3542	−207	5711	−976
	Post op.	3335		4744	
O_4	Pre op.	5132		7716	
	Post op.	—		—	
O_5	Pre op.	2682	−83	4312	−103
	Post op.	2599		4209	
O_6	Pre op.	3229	−234	5274	−188
	Post op.	2995		5086	
O_7	Pre op.	3788	−730	6277	−1502
	Post op.	3058		4775	
Control Patients					
C_1	Pre rest	2680	+176	4250	+119
	Post rest	2856		4369	
C_2	Pre rest	4259	+996	6925	+1291
	Post rest	5255		8216	
C_3	Pre rest	3829	+299	6354	+323
	Post rest	4128		6677	
C_4	Pre rest	3068	−786	4933	−1331
	Post rest	2282		3602	

TABLE 4

Patient		Thiosulfate Space ml	Calculated Change ml
Operated Patients			
O_1	Pre op	17920	−520
	Post op	17400	
O_2	Pre op	11348	−21
	Post op	11327	
O_3	Pre op	12862	+298
	Post op	13160	
O_4	Pre op	17583	
	Post op	—	
O_5	Pre op	11503	−1870
	Post op	9633	
O_6	Pre op	11352	+22
	Post op	11374	
O_7	Pre op	14928	+8453
	Post op	23381	
Control Patients			
C_1	Pre rest	11423	+179
	Post rest	11602	
C_2	Pre rest	43000	−20500
	Post rest	22500	
C_3	Pre rest	14600	+2700
	Post rest	17300	
C_4	Pre rest	13357	−195
	Post rest	13162	

TABLE 5 *Tissue changes per kilo blood, fat free substance*

Patient	Sodium mM	Potassium mM	Chloride mM	E C F ml	I C F ml
Operated Patients					
O_1	+13.9	−25.2	+4.0	+50	−21
O_2	+17.0	−24.5	+0.5	+21	−10
O_3	+1.0	−5.9	−0.6	−5	+1
O_4	+15.5	−3.0	+12.8	+108	−99
O_5	−0.1	−16.0	+1.1	+19	−14
O_6	+15.0	+14.0	+9.5	+87	−88
O_7	−6.5	−9.3	+3.0	+36	−19
Control Patients					
C_1	+4.0	+0.2	+3.7	+31	−55
C_2	+1.9	−5.9	+8.9	+71	−58
C_3	+2.7	−41.0	−1.0	−14	+21
C_4	−11.3	−3.7	+0.9	+5	−19

The serum and blood volume determinations comprise group 2 and are given in table 3. It will be noted that the control patients demonstrate variations in their serum and blood volumes as great or even greater than those observed in the operated patients.

Group 3 includes the extracellular fluid volume or, to be more accurate, the "thiosulfate space" determinations (table 4). It is obvious that the changes in the "thiosulfate space" following transurethral prostatectomy are of no significance in view of the findings in the control patients.

Muscle electrolyte and water analyses are included in group 4; the changes following transurethral prostatectomy in the operated patients and "rest" in the control patients are shown in table 5. Again, these data indicate no significant differences between the patients operated on and the controls.

DISCUSSION

Clinically, none of the operated patients evidenced signs and symptoms of either extracellular or intracellular edema. The essentially unchanged serum electrolytes, hematocrit and protein values following transurethral prostatectomy would seem to indicate no net gain of fluid in the vascular and interstitial compartments from the irrigating fluid or from other body compartments.

Examination of the serum volume determinations in the operated patients reveals decreases ranging from 83 to 730 cc. These values suggest also that there is essentially no gain in vascular water following prostatectomy. Furthermore, the variations obtained in the controls (-786 to $+996$ cc) imply that the method, in our hands, is not accurate for changes less than 1000 cc.

Thiosulfate space calculations were virtually unchanged by operation in four of the patients. In one patient the thiosulfate space was increased by 8453 cc; this was obviously an error since the patient had no other evidences of a marked increase in extracellular fluid. Two of the controls demonstrated no change in thiosulfate space following "rest," one showed an increase of 2.7 liters while the fourth evidenced an increase of 20.5 liters. With variations of this magnitude in the controls, it becomes apparent that the data obtained from the operated patients are of no significance.

Similarly one can attach little importance to the electrolyte and water changes in the tissues of the operated patients since the controls showed variations of the same type and magnitude.

It is believed that this study emphasizes quite pointedly the importance of controls in experiments. On the basis of the controls in this study much of the data obtained have been discarded. It is interesting to note that variations in fluid and electrolyte balance, similar to those presented in this study, have been reported in the literature to occur after anesthesia, thoracic procedures, etc.; none of these studies were controlled. Methods for measuring extracellular fluid volume as well as intracellular electrolyte and fluid in patients, are very inadequate at the present time.

CONCLUSIONS

Transurethral prostatectomy, as performed in this study, has no immediate postoperative effect on the serum electrolytes, serum protein, serum volume and hematocrit of elderly males.

Experimental controls revealed that some of the methods used for measuring intracellular and extracellular fluid and electrolytes are inadequate.

The authors are highly indebted to Miss Madeline McMath for her aid in the chemical determinations.

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EXPERIMENTAL PROSTATECTOMY IN THE RAT

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In 1936 Zawadowsky reported reduction in the weight of the testes, seminal vesicles and prostate glands of young male rats fed ground cocks' combs or injected with an alcoholic extract of comb tissue. Previously, Buckner, Insko, and Martin (1934) had reported that comb removal in cockerels led to larger testes and increased fertility. Zawadowsky confirmed the result of comb removal on testis size and postulated a reciprocal relationship between secondary sex characters such as the comb and the gonads, thus: pituitary $\rightleftharpoons$ testis $\rightleftharpoons$ comb, instead of pituitary $\rightleftharpoons$ testis $\rightarrow$ comb, in which the comb is a passive receptor. Hoskins and Koch (1939), repeating and extending Zawadowsky's experiments, observed no effect on feeding comb tissue to either rats or cockerels, and a general toxic effect following injection of a crude alcoholic extract of comb tissue into rats. However, they did observe that seven months after comb removal, the testes of combless cockerels were significantly larger than those of normal controls. This suggested to them, as it had to Zawadowsky, that a reciprocal testis-comb relationship exists. Hoskins and Koch realized that the part played by the pituitary, as well as the possible influence of light on this action of the comb, required investigation before the mechanism could be interpreted and suggested that such an investigation might reveal a triangular, reciprocal relationship expressed as follows,

$$\begin{tikzcd}
 & \text{comb} \arrow[dl, shift left] \arrow[dr, shift left] & \\
\text{pituitary} \arrow[ur, shift left] \arrow[rr, shift left] & & \text{testis} \arrow[ll, shift left] \arrow[ul, shift left]
\end{tikzcd}$$

rather than the type of relationship suggested by Zawadowsky.

The ability of the comb, a secondary sex organ, to influence the testis excited us to look for a reciprocal relationship in the rat between the prostate gland and the testes. Furthermore, we felt that careful morphological studies of the pituitary glands of prostatectomized rats might reveal the presence of the triangular, reciprocal relationship suggested by Hoskins and Koch. Consequently, we undertook to study weight and cytologic changes in the pituitary and testes of young rats at varying intervals after total prostatectomy. As a corollary, other organs including the seminal vesicles, adrenals, liver, and kidneys were examined.

Since Fischera (1905) noted changes in the anterior pituitaries of cocks following castration, a vast amount of literature has accumulated regarding cytological changes in the anterior pituitary of various experimental animals and man when normal endocrine relationships are disturbed by experimental or disease mechanisms (Bryant, 1930; Martin, 1932; Nicholson, 1936; Fischera, 1937; and Reese, 1939). In castrated male rats increased basophiles and so-

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called "castration" or "signet-ring" cells have been observed almost universally These cells are of the basophilic type with swollen, vacuolated cytoplasm and are interpreted as evidence of possible hyperactivity of these cells

We have found only one reference to experimental work which specifically sought to study prostate pituitary relationship in this manner Howarth (1950) states very briefly that prostatectomy in the marsupial (Trishosurus vulpecula) disclosed no histological abnormalities in the pituitary, testes, adrenals, or thyroid Concerning prostate-testis relationship, Walker (1901, 1911) found that complete removal of the prostate gland in the adult male albino rat had no effect on the histological structure of the testes 4 to 7 months postoperatively and that complete removal of the prostate in the young animal had no effect upon the subsequent development of the testes Strauss (1924) noted that removal of either the seminal vesicles or the prostate had no effect on the libido of the white rat or on the structure or physiology of the testes, and that removal of the prostate is usually followed by atrophy of the seminal vesicles in time Fawlah (1930), using guinea pigs, found no macroscopic effect upon the testes and accessory sex glands after prostatectomy

MATERIALS AND METHODS

The work of Walker (1910) demonstrated that the prostate gland in the albino rat is easily accessible and can be removed *in toto* with low mortality The rat prostate consists of two distinct ventral and two fused dorsal lobes A "coagulating gland" is located adjacent to each seminal vesicle These coagulating glands are histologically not unlike prostatic tissue Accordingly the albino rat was selected as the experimental animal Decision was made at the start of the investigation to remove the prostate completely and leave the seminal vesicles and coagulating glands intact

Normal albino male rats of the Wistar strain, weighing approximately 250 gm, were used for all of the experiments They were kept on a stock diet of Purina dog chow and water *ad libitum* Total prostatectomy was performed as follows

The animal was anesthetized in a large jar with ethyl ether and then weighed A midline lower abdominal incision was made and the intraperitoneal bladder dome identified, grasped with iris forceps and reflected cephalad This maneuver exposed the two large ventral lobes which were then easily removed with another iris forceps The bladder dome and seminal vesicles were then reflected caudad and the dorsal lobes removed with the iris forceps Ligatures are not necessary and complete prostatectomy is accomplished with normal continuity of the urinary tract The entire abdominal wall, including skin, was then closed with one continuous silk suture A sham operation was done for control purposes exactly as above except that the prostatic lobes were handled by the forceps but not removed In one group of control animals, bilateral orchiectomy was done under ether anesthesia by exposing the testes through a transverse scrotal incision and dividing the cord structures between clamps and ligating the proximal ends after removal of the testes

The animals were sacrificed at 30, 60, and 90 days after operation and studies made of the pituitaries, testes, adrenals, seminal vesicles, livers, and kidneys. The last three organs were not conclusively studied because initial observations gave no data pertinent to the basic problem. The pituitaries, adrenals and testes were prepared for cytological study by the method of T. Maxwell, Jr. (1938) and lipid studies by the Oil-Red-O technique outlined by Lynch and Scott (1950).

RESULTS

In the initial group of animals there were 16 prostatectomized, 17 sham-operated controls and 3 castrated controls. They were sacrificed at 60 days following the operations and weighed between 350 and 400 gm. at death. No evidence of prostatic tissue was detectable grossly in any of the prostatectomized animals. This first experiment was done solely for studies of the pituitary cytology, and hence pituitary weights were not determined. The sections were studied under high dry and oil immersion magnifications. In order to evaluate the changes in the anterior pituitary an arbitrary classification was used. The three main categories of cells (i.e., acidophile, basophile, and chromophobes) were studied for qualitative and gross quantitative differences. No cell counts were made. Sections were studied from representative areas throughout each pituitary. Variations in relative number, cytoplasmic differences (granules, vacuolation, etc.) were particularly studied.

The first group of animals showed the following changes in the pituitaries:

A) *Anterior lobe.* 1) Acidophiles: There was no apparent variation in the number, distribution, granularity or staining characteristics of the acidophiles in the three groups. In the castrates there was an apparent decrease in the acidophiles probably because of the obvious increase in basophilic "castration" cells and basophilic chromophobes.

2) Chromophobes: There was no apparent variation in the three groups except more basophilic chromophobes were present in the castrates.

3) Basophiles: The castrates were used as controls in this experiment to compare basophilic changes in them with any possible castration-like changes occurring after prostatectomy. The pituitaries of these castrates showed the typical vacuolated basophiles (castration cells) and definite increase in basophiles and basophilic chromophobes. This occurred in all three animals. In the prostatectomized animals 14 of 16 animals showed the presence of these typical basophilic castration cells and slightly increased basophilia. However, the degree of vacuolation and numbers of these cells were much less than in the castrates. Many of the sections in this latter group showed basophiles with marked variation in the size of cytoplasmic granules as well as vacuolation. Although there were typical castration cells in 14 of 16 prostatectomized animals, only one showed the very marked changes as seen in the castrates. In the sham-operated controls 12 of 17 showed typical basophilic castration cells. None of these latter controls showed the marked changes seen in the castrate and the general impression was that basophilic changes were more marked in the prostatectomized animals than in the sham-operated controls. It is our impression that probably some degree of vacuolation of basophiles is a normal process in the rat. The

TABLE 1

Group	No. of Animals	0	+	++	+++	++++
Prostatectomized	16	2	2	8	3	1
Sham operated controls	17	5	3	5	4	
Castrated	3					3

Code 0 = No "castration" cells
+ = Rare "castration" cells (i.e., 1 or 2 per several sections)
++ = 1-3 "castration" cells per section
+++ = 1-2 "castration" cells per high power field
++++ = Many "castration" cells per high power field

TABLE 2

Group	No. of Animals	Av. Wt. Gain (Grams)	Av. Comb. Test Wt. (Grams)	Av. Comb. Adrenal Wt. (Mg.)	Av. Liver Wt. (Grams)	Av. Pituitary Wt. (Mg.)
Prostatectomized	11	59.3	0.91	22.0	10.3	9.7
Range		(25.0-95.0)	(.70-1.3)	(15.0-29.0)	(8.6-13.3)	(9.0-12)
Sham operated controls	2	67.5	1.15	22.3	10.5	12.5
Range		(55.0-80.0)	(1.05-1.25)	(21.5-23.0)	(10.4-10.6)	(12.0-13.0)
Normal controls	2	82.5	0.85	27.8	11.8	15.5
Range		(75.0-90.0)	(.85-.85)	(27.5-28.0)	(11.6-12.0)	(15.0-16.0)

above results in this first experimental group are not indicative of any obvious specific cytologic change in the anterior pituitary after total prostatectomy.

The study of the basophilic changes in the foregoing group is represented in table 1.

B) *Pars intermedia.* No apparent differences were observed in any of the three groups. Rathke pouch cysts were seen in random animals throughout the series.

C) *Pars nervosa.* No apparent differences were observed in any of the three groups.

From this initial experiment it was concluded that total prostatectomy in the young albino rat causes no peculiar cytological changes in the anterior, intermediate and posterior lobes of the pituitary.

In the second experiment 50 male albino rats weighing between 250 and 320 gm. were used. Total prostatectomy, as just described, was done in 40, sham operation in 5, and 5 animals were maintained as normal, nonoperated controls. These animals were divided into three groups to be sacrificed at 30, 60, and 90 days. The objective in this second experiment was to study pituitaries, testes and adrenals for cytologic and lipid changes with the Maxwell triple stain and Oil Red 0 techniques and changes in gross weight.

The first group was sacrificed at 30 days and consisted of 11 prostatectomized, 2 sham operated, and 2 normal control animals. The data on these animals are shown in table 2.

The differences in this 30 day group are slight and show decreased weight gain and smaller pituitaries by weight in the prostatectomized animals. However, it has been noted in subsequent studies that pituitary weights are extremely variable in the rat and there is no direct correlation with body weight.

The pituitaries, adrenals, livers, kidneys, seminal vesicles and testes in this first group were studied for variations in cellular lipid by the Oil-Red-0 technique and no significant differences were found in any of the organs. The livers, kidneys, and seminal vesicles showed no variation in lipid between the prostatectomized animals and controls. In the pituitaries the anterior and middle lobes were found to be devoid of lipid with this stain. The posterior lobes contained only scattered lipid material within macrophage-like cells. The cortices of all the adrenals were abundant with lipid without variation. The livers of those animals gaining the least weight in the prostatectomized group showed no evidence of increased lipid or fatty infiltration. The testes showed the well-known phenomenon of migration of lipid from Sertoli cells through the spermatogenic cell series as spermatogenesis progressed. Leydig cell lipid was not stainable with this technique and no information could be obtained about lipid changes in them. Testes and adrenals studied with triple stain showed no variations of significance within the groups. Pituitaries were not available for routine studies because they were used for lipid studies.

The group sacrificed at 60 days consisted of 11 prostatectomized, 2 sham-operated and 2 normal controls. The data on these animals are shown in table 3. Studies on the pituitaries in this group of animals showed that there were changes similar to those in the initial group studied and no specific anterior pituitary changes were related to prostatectomy. Table 4 shows the basophilic changes in these 60 day animals according to the code used in table 1.

These basophilic changes showed the previously noted nonspecific effect. There was a slight tendency towards more basophilia in the prostatectomized animals but generally the changes were not remarkable. No differences were noted in the acidophiles and chromophobes.

TABLE 3

Group	No. of Animals	Av. Wt. Gain (Grams)	Av. Comb. Test Wt. (Grams)	Av. Comb. Adrenal Wt. (Mg.)	Av. Liver Wt. (Grams)	Av. Pituitary Wt. (Mg.)
Prostatectomized	11	96.9	1.49	16.9	12.5	8.0
Range		(45.0–140.0)	(1.25–1.8)	(13.5–19.5)	(9.2–14.4)	(6–10)
Sham-operated controls	2	135.0	1.55	21.0	14.9	10.5
Range		(130–140)	(1.35–1.8)	(20–22)	(13.8–16)	(10–11)
Normal controls	2	90.0	1.55	15.3	12.8	7.5
Range		(80–100)	(1.5–1.6)	(15–15.5)	(11.5–14)	(7–8)

TABLE 4. *Animals sacrificed at 60 days*

Group	No. of Animals	0	+	++	+++	++++
Prostatectomized	10	1	1	5	2	1
Sham-operated controls	2		1		1	
Normal controls	2	1		1		

Note: In prostatectomized group one pituitary not obtained when sacrificed.

TABLE 5

Group	No of Animals	Av Wt Gain (Grams)	Av Comb Test Wt (Grams)	Av Comb Adrenal Wt (Mg)	Av Liver Wt (Grams)	Av Pituitary Wt (Mg)
Prostatectomized	10	112 8	1 28	20	12 9	12 6
Range		(65-185)	(1 05-1 55)	(17 5-23)	(9 9-15 1)	(11-16)
Sham operated control	1	120	1 55	22	11 9	11 9
Normal control	1	140	1 55	22	12 5	11 0

The testes and adrenals were again studied with the Oil-Red 0 and triple stain technique and no variations were noted

The remaining animals were sacrificed at 90 days (table 5) There were 10 prostatectomized, 1 sham-operated and 1 normal control The data in table 5 show no specific weight variations in any of the groups The pituitaries were studied with the Maxwell stain and again there were the nonspecific changes already described in the anterior pituitaries and no specific changes related to total prostatectomy

Studies of the testes and adrenals of this 90 day group with the Oil-Red 0 and Sudan IV techniques revealed no unusual changes in the intracellular lipid in these organs Here also, lipid material in the Leydig cells could not be demonstrated by use of these two dyes

DISCUSSION

In this group of experiments, the effects of total prostatectomy on other endocrine organs, particularly the pituitary, testes, and adrenals, have been studied in the young male albino rats The evidence obtained in these series of comparatively few animals indicates that there is no apparent specific effect on the weights or cytological picture of the livers, kidneys, pituitaries, adrenals, testes and seminal vesicles after the prostate gland is completely removed That the removal of a single end organ such as the prostate gland should produce any changes in pituitary, testes or adrenals is a matter of conjecture For example, it *is* quite possible that the other end organs receiving stimulation from the testes, such as seminal vesicles, coagulating glands and even the penis and larynx, must also be removed completely before the pituitary-testis end organ cycle is disrupted enough to produce definite changes Removal of the prostate alone apparently does not affect this cycle

SUMMARY

Total prostatectomy in young (250 gm) rats produced no specific weight or cytological changes in the hypophysis, testes, adrenals, liver, kidneys or seminal vesicles at 30, 60, and 90 days after operation Also, no apparent lipid changes were *noted histologically* in these organs

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URIATRY: A CONCEPT

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In a study of cases of urogenital lesions at Patton State Hospital (California Department of Mental Hygiene) it was found that some of these patients presented such a complex clinical picture that the lesions were not discovered by initial examination, misdiagnosed or given belated or inadequate therapy. This was true even when psychosomatic factors were considered in patients with complex clinical pictures. There were symptoms present at the time of examination which were due to disturbances of other organic systems and created an uneven, confused and apparently misleading clinical and psychosomatic picture.

It became important, therefore, to attempt to classify these symptoms of divergent clinical and pathological manifestations into one syndrome in order to better identify and treat urogenital lesions. If we place in the center of these complexes, the common denominator, the initial urogenital component, we thereby stress a uniformity in correlating diversified symptoms even if the total clinical picture is far removed from the consequences of urogenital disturbances. This can be expressed by using the concept of uriatry, stressing thereby the physician's part of it.

It is assumed that the primary factor of the disturbances in these observed cases is a urogenital one. This component of the clinical picture is so well camouflaged by the many symptoms derived from manifold causes that it must literally be dug out to arrive at the uriatric concept. It would be very simple to regard these symptom complexes as an end process of a urologically missed lesion, but this would not uncover the entire picture.

We must therefore widen our point of view. We should regard the whole patient as a clinical entity and avoid the pitfall of seeing only through the magnifying glass of the organ specialist. We must acknowledge, when reviewing such complex clinical pictures, that very often there can be an overlapping relationship between urology and other medical branches. Psychiatry, as such, is the "filler in."

The expression, uriatry is an approach to this new concept. It is used solely as a methodological concept even if the term may be regarded by some as unnecessary.

What is the mechanism of uriatry?

It must be assumed that the initial organic lesion of the urogenital system is a dynamic cause, a trigger mechanism. If this is not properly attended, it elicits a process of adaptation. In line with this adaptation a morphological, or organic, disturbance or adjustment follows. On the bases of the behavioral, or the psychological pattern of the individual, this elicits emotional tension, which, in turn, may influence any vegetative system.

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The various vegetative responses appear in the different vegetative functions with multiple and manifold symptoms. And, if to these symptoms are added iatrogenic interferences (either with positive or negative results), the clinical picture may be a most confusing one.

The urological aspect, until now, is divided according to the different medical branches. This division is convenient for study, but it appears to be insufficient and disturbing from the clinical point of view when we regard the whole aspect of the individual organism.

As uriatry comprises this whole clinical complex we should, rather, speak about gynecologic, pediatric, psychiatric, ophthalmologic, geriatric, oncologic, etc. uriatry, and not speak of "urology," which strictly analyzed, pertains to the lesions of the genito-urinary organs only.

With the conception of uriatry, we are able to cover not only the field of the psychic influences on micturition, but also the territory of psychic disturbances due to organic genito-urinary causes.

CASE ABSTRACTS

To substantiate this concept, the following abbreviated case histories have been selected from the abundant clinical material at the hospital. In these cases the most conspicuous symptoms have been due to mental disturbances, although the initial lesions appear to have been genito-urinary.

Case 1. M. M., a 35 year old white nurse, who was referred to urology because of "hematuria", was found to have ruptured villi of the internal vesical orifice. She was a habitual drug addict.

The surgical scars on the abdominal wall, the result of 12 major operations (fig. 1) aroused interest. After considerable investigation her history revealed that at 6 years of age she had scarlet fever with "kidney complications on the right side." At sixteen she had an appendectomy because of pains in the right side, followed by peritonitis.

Because of "bowel obstructions" she had separation of adhesions at eighteen and again at twenty. After the latter operation, a diagnosis of tuberculous peritonitis was made. Her recovery was stormy, complicated with renal insufficiency, which necessitated a urological examination. It was found she had an anomalously inserted ureter into the right kidney pelvis. A renal pelvic plastic operation was performed (age 22) which was followed by pneumonia and a perinephric abscess, which was drained.

The following year a right nephrectomy was performed because the plastic operation had not been successful. At the time it was found that she had a Bacillus abortus infection of the left kidney. After one of the many ureteral catheterizations, a paranephric abscess developed on the left side and was surgically drained.

Because of an obstructive ileus, based on intra-abdominal adhesions, she underwent a resection of the bowel performed by absolutely reputable surgeons, at the ages of 29, 30 and 31.

She tried to justify her drug addiction by saying that "before and after these

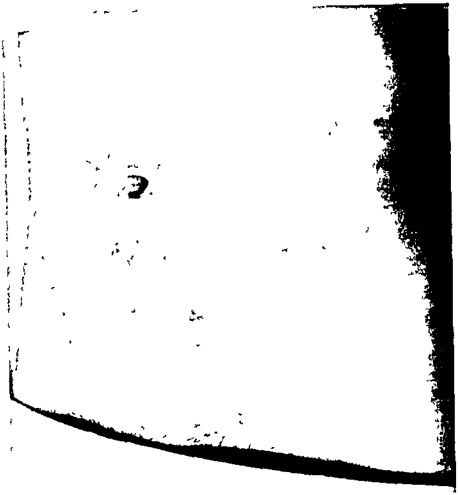

FIG. 1

many surgical procedures, I was in constant pain and I just wanted to be well."

Comment: It appears that the congenitally anomalous right kidney elicited symptoms which led to an appendectomy with intra-abdominal complications. The multiple surgical interferences brought personality changes, one phase being her drug addiction.

The symptoms of this uriatric patient could be classified, if each were taken independently at a specific time, as surgical, internal medical, tuberculotic, psychiatric or urologic. From the uriatric point of view, they are only a part of this broader concept.

Case 2. R. F., a 74 year old white man, who several times attempted suicide, was melancholic and depressed. He complained that there was no medication for "that old cancer in my breast" pointing to his enlarged breasts, which started with treatment of his prostatic troubles.

Nine years ago he underwent transurethral prostatic resection; the following year, bilateral orchiectomy. Since that time he had been intermittently on stilbestrol medication.

Examination showed (fig. 2) a feminine fat distribution (enlarged breasts, etc.) soft skin, pubic hair change, and a scarce beard growth ("I stopped shaving"). The circumference of the right leg was enlarged. The prostate was stone-hard and indurated. Osteoblastic changes were found in the lumbar and thoracic spine. The serum acid and alkaline phosphatases were increased.

Comment: The castration and intensive estrogenic medication influenced both his metastatic prostatic cancer and his body constitution by feminizing this 74 year old man. This appears to have been elicited by a psychotic disturbance, a reactive depression, with melancholia, which clinical picture was in the foreground.

In this uriatric patient symptoms of psychiatric, oncologic, endocrine and urological disturbances have been present.

Case 3. D. B., a 20 year old white man, was referred because of urinary retention.

He was mentally disturbed, sullen, morose, and told rather fantastic stories about urological treatment, especially following his recent urological operation.

His kidney function was impaired (phenolsulfonphthalein output in 2 hours only 12 per cent); the nonprotein nitrogen was 125 mg. per cent. The blood pressure was 210/115. Eye fundus examination showed extensive areas of "cotton wool" exudates throughout the retina, with suggestive papilledema with optic atrophy.

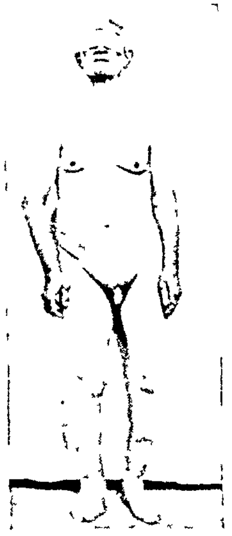

FIG. 2

Because of "renal disease" he was urologically examined at the age of 3 months and again at 10 years. (The diagnosis was bilateral hydronephroses and hydroureters, but no treatments were instituted at that time.)

Because his urinary stream was diminishing, he had a complete urological examination. This revealed that the anterior lobe of the prostate was enlarged, the bladder atonic and trabeculated, with a deep bas fond and 180 cc residual urine. The pyelograms revealed bilaterally bifurcated kidney pelves, with a lateral take off of the ureters, but no polycystic kidneys. The ureters were dilated.

After removal of 10 gm. of the anterior prostate lobe transurethrally, visual difficulties developed and the patient became mentally more disturbed.

Comment: Failure to correct these congenital urogenital malformations at an early age produced an advancing kidney insufficiency. This preuremic state was influenced by the stress of operative interference, at this late stage, manifesting itself in a psychosis and visual disturbances Although these symptoms have been in the foreground in his clinical picture, the fundamental disturbance was a urological one.

The symptoms of this uriatric patient have been psychiatric, medical, ophthalmologic and urologic.

Case 4. A. S., a 22 year old white woman, attempted suicide twice, once after a cystocele operation. She complained of pain on urination, and urgency and frequency.

She was raped at the age of 13 with consequent cystopyelitis. She was married at 15. Her husband abandoned her during her pregnancy at the age of 17. At 19 she married a 34 year old man. Since that time her urinary symptoms were aggravated considerably, especially after coitus.

On cystoscopic examination, a stricture of the right ureter was found. Previous to this diagnosis (because of pain on the right side), she had undergone appendectomy, uterine suspension and right salpingectomy.

It was found that she had a number of psychoneurotic components, too, such as hysteria, hypochondria and reactive depression, which led to her suicidal attempts.

Comment: The initial urogenital lesion was defloration cystopyelitis, followed probably by the ureteral stricture. The symptoms of this lesion led to surgical polypragmasia, which aggravated the latent psychoneurotic mental factor and led to her disturbed personality.

This uriatric patient had gynecological, sexological, psychiatric and urologic symptoms.

Case 5. V. K., a 32 year old white male drug addict, was a bed wetter until the age of 8. At 17 (in 1939) he suffered a bomb blast in England with a consequent pain on the right side, which necessitated an exploratory laparotomy, but no explanation was found for the pain. As it continued, in 1941 (age 19), a right nephropexy was performed with subsequent postoperative infection and drainage. From then on he had frequent attacks of ureteral colic on the right side. Finally, in 1946, the ureteral calculi were removed cystoscopically. It was during this time that the narcotic habit developed.

In 1946 he was in a train wreck and his right kidney tore loose again. It was resuspended. Postoperative infection developed and a perirenal abscess was drained 5 months afterward. Since that time he has had a mixed colon type pyelonephritis on the right side, with frequent ureteral spasms. Finally, in 1950 he underwent a right nephrectomy. (He also had a resection of the bladder neck during one of his 27 cystoscopies.)

At present examination he suffered from a strictured prostatic urethra, a definite median bar of the bladder neck with a nonspecific infection of the lower tract, extending into the right ureteral stump and painful peri-ureteritis.

Comment: The bomb blast started the process. Due to ptosis of the right kidney, with stasis and stone formation, the patient had been subjected to frequent surgical interference.

The sufferings because of the ptosis led the already labile psychotic personality (his bedwetting) to deeper disturbances, with consequent addiction.

This uriatric patient had symptoms which can be classified as general surgery, psychiatry and urology.

Case 6. B. S., a 59 year old white man, was classified as a sexual psychopath. He had continuous urinary urgency, with dysuria, which made him irritable and uncooperative. Two years ago he had a right nephrectomy because of a tuberculous kidney. Previously he had an appendectomy.

Examination showed a contracted bladder of 100 cc capacity, and some ulcerations on its wall. The prostatic urethra was rigidly strictured and tilted anteriorly. The left epididymis was tender; the left seminal vesicle was hard. The left kidney function was decreased (phenolsulfonphthalein only 38 per cent in 2 hours), and its infundibula were narrowed. Tubercle bacilli were found in the urine.

In his childhood the patient was "sickly and high strung," rather intellectual, and "suffered always from frequent urination." His urinary disturbances led him to early masturbation. At the age of 9 he started to rubbing his penis against young girls' genitalia. He had his first heterosexual experience at 17. He was married at 24, but divorced as his wife was "not interested and sickly." He fondled little girls (in his estimation at least 150) but denied any penetration whatsoever.

Comment: His inflammatory (probably tuberculous) urinary disturbances predisposed him to early sexuality. As his physical constitution (because of early tuberculosis?) was under par, the stress of livelihood, and marital disturbances, led him into compensatory activities. First he became an excessive alcoholic. Later, diverting from this for his satisfaction, he transferred to the sexual sphere, seeking to relive the pattern of his early experiences.

As his genito-urinary tuberculosis was apparent, surgical polypragmasia was not successful.

SUMMARY

For evaluating pathological manifestations of different organ systems, where the initial lesion is urogenital, the concept of uriatry is introduced.

Uriatry is a reorientation, designed to express a uniform clinical point of view.

The author wishes to express his appreciation of the assistance of Otto L. Gericke, M.D., Superintendent and Medical Director of the Hospital, in carrying out this work.

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A NEW DEVELOPMENT FOR LIGHT BEARING SURGICAL INSTRUMENTS

HENRY BODNER, ALLAN H. HOWARD AND JOSEPH H. KAPLAN

Since the discovery of the incandescent lamp, there has been marked improvement in the illumination of many surgical instruments. However, the current power source for these incandescent lamps has changed very little over the years. The dry cell battery and the direct current rheostat are unchanged from that of the original instrument except for refinements in battery boxes, sterilizable cords and rotary connectors. The large, cumbersome battery box and the light cord may be eliminated by applying directly to the cystoscope a small, long-acting battery enclosed in a plastic case.

Alesandro Volta was the magician who in 1799 first imprisoned the spirit of electricity so that it could be carried around and used where most convenient. He discovered that electric current could be produced by chemical action. He used two plates made of different metals submerged in an acid of a salt solution connected through a wire to construct his first effective cells. In 1868, George Leclanche invented a cell bearing his name which became the basis of most of the batteries used today. In the Leclanche cell, a carbon rod, the negative terminal, takes the place of Volta's copper plate. The electrolyte consists of a solution of sal ammoniac instead of acid. The distinctive feature of the cell is the use of a mixture of manganese dioxide in carbon grains packed around the carbon terminal to act as a "depolarizer," by absorbing the hydrogen before it has a chance to form the objectionable film on the positive terminal. From this time on it was found that by using various degrees of resistance one could control the amount of current obtained from batteries. In the earlier days of cystoscopy, the cystoscopic cord consisted of two wires encased in a cloth sheath. As time progressed, the cloth sheath was replaced by more suitable nonconductible material, rubber primarily, so that the cystoscopic cord could be sterilized in a cold sterilizing solution.

There are at least 18 contact points or connections which may become sources of difficulty between the dry cell battery and the light bulb in the cystoscope. The contact points are: 1) batteries hooked up in series, 2) connections to rheostat, 3) contact points in the rheostat, 4) contacts of the cystoscopic cord from the battery box or rheostat, 5) the soldered cystoscopic wire to the contacts, 6) the soldered cystoscopic wire to the adapter at the end of the cord, 7) the adapter to the rotary connector, 8) the rotary connector to the cystoscope, 9) the cystoscope wire to the bulb contact.

By connecting the rotary connector directly to the new, small, battery apparatus and eliminating the rheostat and the cord, one immediately loses at least 10 important points of contact and potential points of mechanical failure. The dangling and troublesome cystoscopic cord draped over the patient is also eliminated.

Read at annual meeting, American Urological Association, New York, N. Y., June 3, 1954.

The initial models we have been using consist of a rectangular plastic case approximately 5.5 cm. by 6.5 cm. by 2 cm. in size, and a cylindrical case approximately 6.5 cm. high and 4.2 cm. in diameter, weighing approximately 125 gm. when filled with the energizing unit. This unit consists of three mercury cells wired in series, giving a total output of approximately three volts when in use.

The mercuric oxide cell described by Samuel Ruben is energized by an electrochemical reaction between the anode (amalgamated zinc) and the depolorizing cathode (mercuric oxide) aided by the cell electrolyte (potassium hydroxide saturated with a zincate). Double nickel plated steel jackets are utilized as the container unit. The batteries are designed to afford maximum protection against the common battery problem of swelling or bulging. A relatively steady voltage of current discharge is characteristic of these batteries, and therefore, are ideal for use in cystoscopic equipment or other light bearing surgical instruments requiring a steady voltage or current supply. There is a rapid drop of current when the battery has lost its capacity so that one knows it is time to discard the battery. The previously used types of batteries under intermittent or continuous discharge have a progressive decrease in their capacities. This is not true of this type of light cell. These batteries, in addition, do not need rest periods in order to maintain operating efficiency. There is a uniform power of output continuously throughout the extended life of the battery. The size of the individual cell (No. 502 cell by Mallory) is .538 inches in diameter and 1.950 inches high, volume of .44 cubic inches and a weight of 1.05 ounces. Three batteries in series, of course, would be three times this amount. These batteries may be recharged when the capacity is lost.

FIG. 1

The mercury battery has a service life of roughly three to five times longer than that of the similar batteries on the market today. The RM 502 cells as manufactured by the T. R. Mallory Co. have a continuous use service life of approximately seven hours. Following constant current drain on one cell there is a drop in the voltage to 2.7 volts which is still sufficient to maintain the lighting of the cystoscope, but is not satisfactory for extremely accurate visualization. The service life of three of the RM cells with interrupted use for cystoscopic procedures is approximately 15 hours.

DISADVANTAGES

The added weight of the "lite cell unit" (batteries enclosed in a plastic case) applied directly to the cystoscope is undesirable. However, three cystoscopists utilizing this equipment found that the added weight factor was a negligible problem. The other disadvantage is the shorter life of the light cells in comparison with the large, dry cells in the battery boxes as maintained by most hospitals. However, the batteries are of such small size and have such long storage life that hospitals and one's own office may readily store additional batteries for use when the old ones are run down. There is approximately a 7½ per cent loss of capacity in the battery *after* 12 months of storage. This does not appreciably affect the lighting characteristics of the cystoscopic bulb or other light bearing instruments. These batteries do not deteriorate or lose their energy appreciably during long storage periods even under the most adverse climatic conditions.

ADVANTAGES

The mercury batteries yield as much as three to five times the energy of other types of batteries. Conversely, the same energy can be provided in one-third to one-fifth the space. There is, also, an appreciable reduction in weight of the mercury batteries as compared with other batteries requiring the same energy to volume and weight. The usual voltage requirement for most cystoscopic procedures varies between 2.9 and 3.2 volts. The capacity under intermittent and continuous discharge at specified loads of one type of mercury cell is demonstrated on the slide. The current source of three of these batteries in series with resistance is fixed between 2.9 and 3.2 volts. With a fixed current source at the maximum, the rheostats are eliminated entirely. This safeguards excessive current accidentally to bulbs thus insuring longer life for the cystoscopic bulb. Of utmost importance is the decrease of contact sources and source of light failures. The cystoscopic cord and the never-ending need of resoldering wires to contact is entirely eliminated. One merely clips on the "lite cell" to the surgical instrument. The cost of this unit should be at least half that of the cystoscopic cord, battery box, batteries, etc. The maintenance cost, also, should be minimum in comparison to the older methods of much more cumbersome equipment.

Utilizing the "lite cell" unit, we performed hundreds of cystoscopic procedures over the past 3½ years. We did, however, record the statistics of 113 office cystoscopic procedures. The total time the cystoscope remained lighted during the procedures was 765 minutes or roughly 12.75 hours. The average cystoscopic procedure was 6¾ minutes. It was our belief that inaccuracies in timing this procedure, for example, testing the cystoscope before use etc., accounted for approximately another two hours of use with one such "lite cell unit."

RESULTS

Adequate and bright lighting of the cystoscopic bulbs were maintained for this period of time described. One cystoscopic bulb required replacement during these 113 procedures. The cystoscopist quickly and readily adjusted himself to the added weight of the "lite cell." The number of light failures, searches for reasons for light failures, repairs and replacement of cystoscopic cords etc., were all eliminated.

CONCLUSIONS

By utilizing three Mallory mercury batteries in series enclosed in a plastic case and applied directly to the cystoscope, adequate lighting is maintained for a period of approximately 15 hours of interrupted use. The size of the individual battery is .538 inches in diameter, 1.950 inches high, and weighs 1.05 ounces. The weight of the light cell unit is approximately 3.5 ounces. The authors performed 113 cystoscopic office procedures utilizing one such light cell unit. The three cells in the series have an output of 2.9 to 3.2 volts which is optimum range required for lighting of cystoscopic bulb. With a maximum fixed current source longer life is given the cystoscopic bulb and the cystoscopic cord is eliminated entirely. The electrical contact points which may be the source of light failures are eliminated. A rheostat is also eliminated. There is a rapid drop of current when this type of battery has lost its capacity so that one knows it is time to discard the apparatus. The large, cumbersome battery boxes with rheostat and cystoscopic cords are entirely eliminated. The unit may be readily adapted to other light bearing surgical and diagnostic instruments. Still smaller batteries manufactured from atomic material and further improvement of present models should demand the elimination of troublesome battery boxes and cystoscopic cords.

ADDENDUM

It recently has come to our attention that a mercury battery apparatus was described at the First International Congress of Broncho-esophagologists in Rio de Janeiro in September 1952 by Dr. Edwin N. Broyles of Baltimore in a paper entitled, "Visual Aids to Broncho-Esophagology," and printed in the transactions of the meeting. We quote from Dr. Broyles' paper:

"... I would like to show a small mercury battery that can be used with the telescopes and which we hope later to be able to adopt to laryngoscopes and the other endoscopic tubes. The A.C.M.I. in New York City is most co-operative in the development of visual aids and is the manufacturer of these instruments."

6333 Wilshire Blvd., Los Angeles, Calif.

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Ruben, S.: Trans. Electrochem. Soc., **92:** 183, 1947.

The Journal of Urology
Vol 73 No 5 May 1955
Printed in U S A

USE OF POLYETHYLENE TUBING IN PRESACRAL PNEUMOGRAPHY

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In 1947 Ruiz Rivas[1, 2] introduced the presacral approach for the induction of retroperitoneal pneumography Since then numerous authors have attested to the safety of this procedure and its value in the roentgenographic demonstration of the kidneys, adrenal glands, spleen and liver It has also been found to aid in the demonstration of primary and metastatic midline retroperitoneal neoplasms

Recently we have found that by using a polyethylene tube (fig 1) for the delivery of the air or oxygen into the presacral tissues, some of the common difficulties associated with this procedure are eliminated The use of the tubing is much more convenient for the operator and more comfortable for the patient It eliminates the need for the continued presence of a needle in the retrorectal tissues and the necessity for repeated or continuous rectal examination to insure the proper position of the needle The tubing greatly facilitates the injection of air or oxygen under fluoroscopic guidance and enables the patient to be moved with greater ease so that the gas may be delivered to the desired area If fluoroscopy is desired, the tubing may be inserted outside the radiology department and the patient then transported to the fluoroscopic room for the necessary studies

EQUIPMENT REQUIRED

Eighteen inches of No 50 polyethylene catheter tubing sterilized in usual manner

No 16 three inch needle
Three way stopcock
One 50 cc syringe
One inch No 22 hypodermic needle
Local anesthesia tray
Gloves, sterile towel for drapes, skin antiseptic, etc

TECHNIQUE*

With the patient in the knee chest position, the skin adjacent to the tip of the coccyx is cleaned and infiltrated with a local anesthetic A 3 inch 16 gauge needle is inserted just distal and slightly to one side of the tip of the coccyx and directed obliquely upward, inward and forward in such a manner that its point

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Accepted for publication October 7, 1954

[1] Ruiz Rivas M Nueva tecnica de diagnostico radiografico aplicable a organos y estructuras ret [illegible] y cervicales Rev clin espan 25 206 1947

[2] Ruiz [illegible] diagnosis generalized subserous emphysema through si [illegible] ure, Am J Roentgenol 64 723, 1950

* The use of a somewhat similar technique was reported by Dr Hans H Zinsser in *Archives of Surgery* 69 736 1954

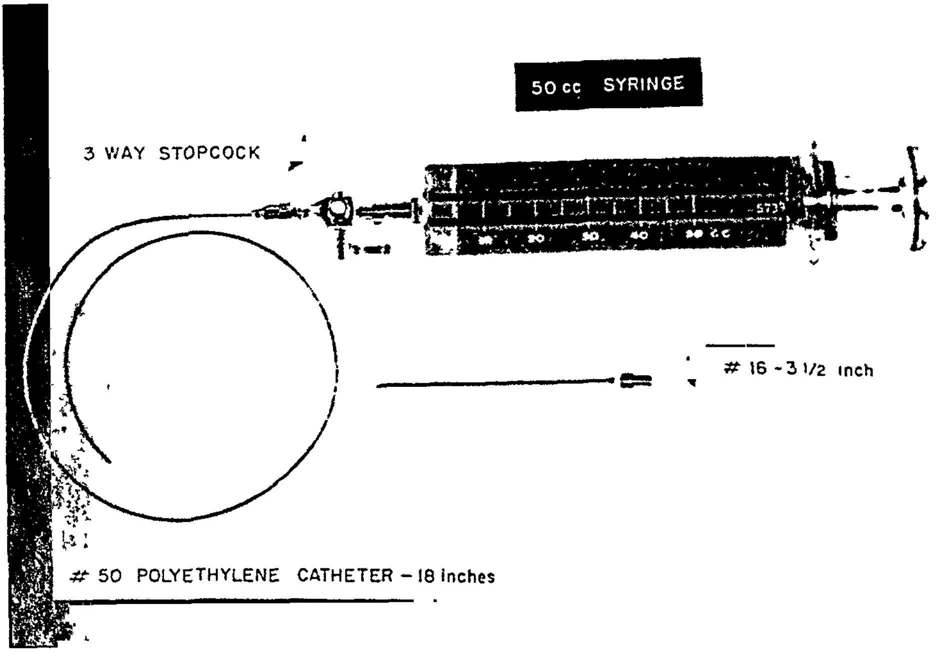

Fig. 1. Equipment required for presacral pneumography with polyethylene tubing

comes to rest in the retrorectal fatty areolar tissue. An examining finger in the rectum is used to palpate the point of the needle and insure its proper position. An 18-inch length of No. 50 polyethylene tubing is threaded through the needle as far as possible, the latter carefully removed, and the tubing strapped to the patient. A 1-inch No. 22 hypodermic needle serves as a satisfactory adaptor between the tubing and 3-way stopcock. Following preliminary aspiration to make sure that a blood vessel has not been entered, air or oxygen is injected.

By rocking the fluoroscopic tilt table, or turning the patient from side to side the gas may be guided into the desired location during fluoroscopy. Supine anterior-posterior and lateral films are taken, the patient removed from the table with the catheter in situ. These are immediately developed and, if satisfactory, the catheter is removed. If not, more gas may be injected as required.

CONCLUSIONS

A modified method of retroperitoneal air or oxygen insufflation by the presacral route has been described. The method involves the use of a polyethylene tubing for the delivery of the gas. This technique is admirably suited for use with fluoroscopy.

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A DIAGNOSTIC AID FOR VISUALIZATION OF THE LEFT SUPRARENAL SPACE

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Ability to diagnose early renal tumors as well as variations in the size and shape of the adrenals has been significantly improved by the use of gas (oxygen or air) injected into the retroperitoneal space by the precoccygeal route. However, difficulties remain; confusing shadows are found more often on the left than on the right side. The contracted fundus of the stomach is a frequent cause of radiodensity in the left suprarenal area. Introduction of air into the retroperitoneum tends to accentuate this shadow rather than eliminate it. This study was undertaken by one of us (L. S.) in an effort to eliminate this troublesome shadow by gaseous distention of the stomach.

Anatomically the fundus of the stomach is anterior to the left suprarenal space. The peritoneum of the omental bursa separates it from the left adrenal gland. The left adrenal gland is slightly larger than the right and lies above and in front of the upper pole of the kidney. Posterior to the gland is the crus of the diaphragm.

The roentgen shadow of the contracted fundus of the stomach is oval in shape (fig. 1, *A*). Its size varies, although it rarely exceeds 4 to 5 cm. in diameter. It lies above and slightly lateral to the left kidney. The position is not always constant and it may appear in the region of the left adrenal gland (fig. 1, *B*). Following introduction of gas in the presacral space, the fundus may be more pronounced (fig. 1, *C*). An example of a situation where gaseous distention of the stomach was useful is demonstrated in figure 2.

TECHNIQUE

Gaseous distention of the stomach for the elimination of troublesome shadows is a simple and effectual procedure. It is usually done concomitantly with the last film in the pyelogram series, the patient having been prepared as usual for pyelography. In addition he receives nothing by mouth for a period of 5 hours prior to the test.

The gas producing agent is composed of two principal ingredients, sodium bicarbonate and tartaric acid. The bicarbonate liberates carbon dioxide when in contact with the hydrochloric acid of the stomach and the ingested tartaric acid. A half teaspoonful of each agent is placed into separate glasses with an ounce of water. The sodium bicarbonate is taken first, followed by the tartaric acid. A roentgenogram is immediately obtained. In order to emphasize the soft tissue densities, the intensity of the exposure is lowered. At times the patient may feel uncomfortable and retch for a few seconds after swallowing the gas producing agent.

Read at a meeting of the Brooklyn Urologic Association, April 1954.
Accepted for publication July 29, 1954.

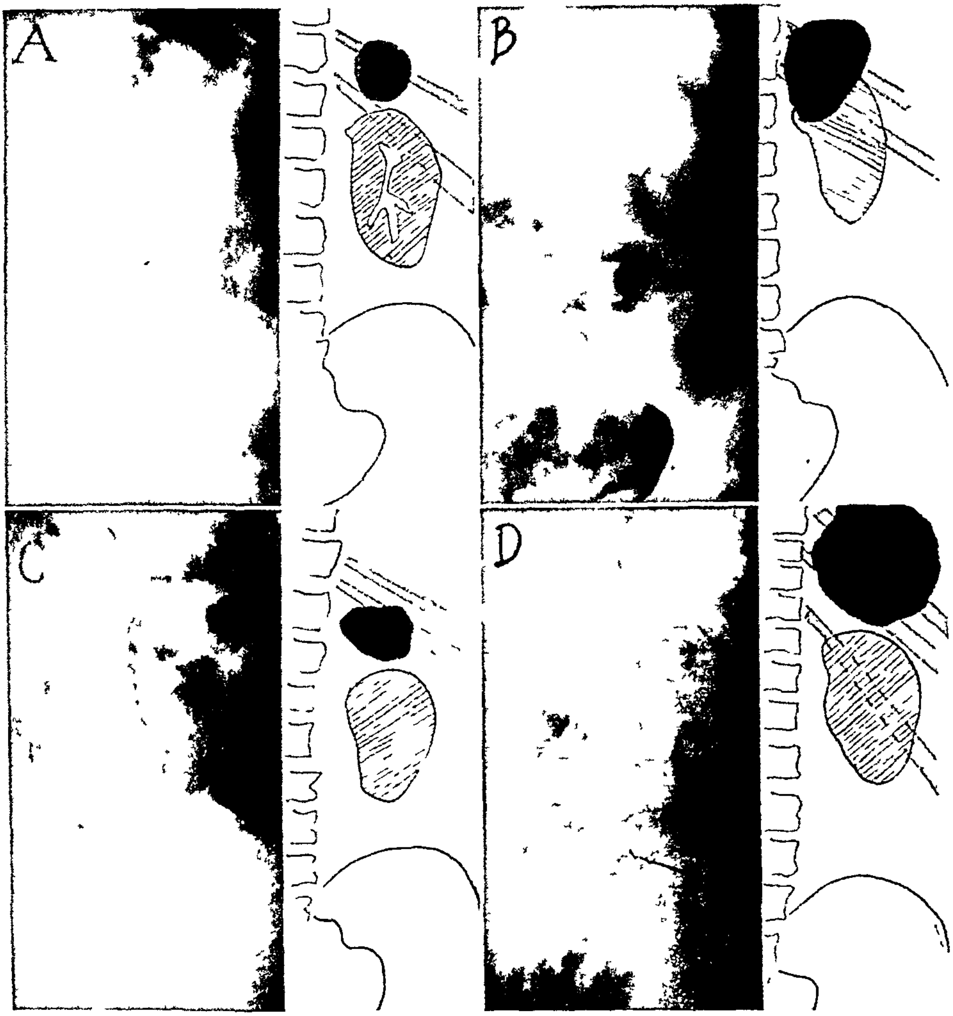

FIG 1 *A*, usual position and shape of shadow of contracted fundus of stomach is demonstrated *B*, contracted fundus is present in region of left adrenal gland. *C*, shadow of fundus is exaggerated by introduction of air *D*, unusually large radiodensity above left kidney caused by fundus of stomach.

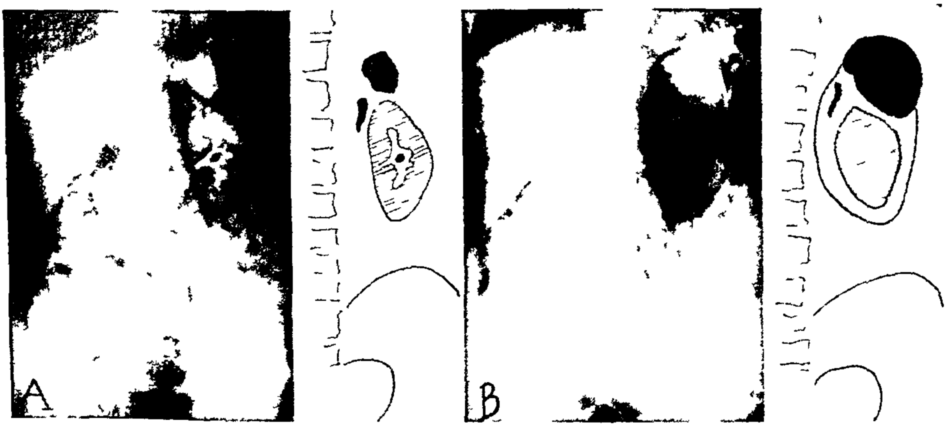

FIG. 2. *A*, 63 year old woman with hirsutism and hypertension. Perirenal air was indicated Oval density was constant in all studies and confused interpretation. Larger density above kidney is fundus of stomach; smaller shadow medial to upper pole is adrenal.

B, distention of stomach eliminated shadow and clearly illustrated left suprarenal space. Shadow considered composite density of fundus and spleen.

DISCUSSION

Left suprarenal densities are commonly encountered Unless accurately identified their presence may initiate a long series of unnecessary diagnostic tests The differential diagnosis for a shadow in this area should include the contracted fundus of the stomach in addition to adrenal tumor, and abnormally placed spleens or accessory spleens, cysts and malignant tumors of the upper pole of the kidney The shadow of the fundus can be eliminated by simply distending the stomach with gas It is our belief that distention of the stomach, combined with perirenal air studies, will clearly demonstrate the left suprarenal area exclusive of all shadows except for the adrenal gland, kidney and spleen

SUMMARY

A useful adjunct for the diagnosis of left suprarenal densities is distention of the stomach The technique and indications for the procedure are discussed

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THE EFFECT OF SEVERAL UROLOGICAL IRRIGATING FLUIDS UPON THE CLOTTING TIME OF PLASMA AND THE TENSILE STRENGTH OF FIBRIN CLOTS

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From the Research Division, Cutter Laboratories, Berkeley, Calif.

The necessity for a careful selection by the urologist of an irrigating fluid for transurethral resection and other intravesical operations has become well established. Such a fluid should be optically satisfactory, nonhemolytic, and nonelectrolytic. Several irrigating fluids have been developed for this purpose, one of which is marketed under the trade name of cytal.* This fluid has been employed in diluted form as an irrigating solution during the performance of the operation and also postoperatively. Recently Schulte et al.[1] have reported its use also in the concentrated form, to prevent firm clots if bleeding becomes excessive, and to soften clots which have formed in the bladder postoperatively so that they can be removed easily by irrigating through the inlying catheter. In view of these recent clinical findings, it was decided to study *in vitro* the effect of cytal on the coagulation properties of human plasma and on the tensile strength of human fibrin clots, and to compare cytal with other commercially used irrigating fluids in this regard. Since cytal in the concentrated form appears to be most effective clinically in preventing and breaking up firm clots, its effect was studied in this undiluted state.

Four fluids—water, normal saline, saturated boric acid, and concentrated cytal—were studied from the following standpoints: a) their effect upon the clotting time of various dilutions of human plasma, and b) the tensile strength of fibrin clots formed from solutions of human fibrinogen.

EXPERIMENTAL

Various dilutions of normal human plasma were made. Their clotting times were determined by adding 0.1 cc of the diluted plasma to 0.3 cc of a "reaction mixture,"[2] which supplies a source of thromboplastin and calcium to allow conversion of the plasma prothrombin to thrombin. The results are recorded in table 1.

In order to ascertain the effect of the irrigating solutions on the tensile strength of fibrin clots, the method of Neurath, Dees and Fox[3] was used. Fibrin clots were formed in 1 by 7 cm. glass tubes by combining 50 cc of a solution of human fibrinogen in the fluids tested with 1 cc of 2 per cent calcium chloride and 1 cc of a 22 units/ml solution of human thrombin in saline. After 1½ hours the clots were removed and stretched in the apparatus illustrated in figure 1. The per cent clottable fibrinogen was determined by a method used by us on plasma.[4] It will be

Accepted for publication June 23, 1954.

* Formula: (Gm. per 100 ml sterile distilled water) sorbitol, 2.73; mannitol, 0.546; methylparahydroxybenzoate, 0.0005; propylparahydroxybenzoate, 0.001; butylparahydroxybenzoate, 0.0001. Manufactured by Cutter Laboratories, Berkeley, Calif.

[1] Schulte, T. L., Hammer, H. J. and Reynolds, L. R.: J. Urol., **71:** 656–659, 1954.

[2] Ware, A. G. and Seegers, W. H.: Am. J. Clin. Path., **19:** 471, 1949.

[3] Neurath, H., Dees, J. E. and Fox, H.: J. Urol., **49:** 497, 1943.

[4] Hidalgo, J., Fowell, A. H. and Ralls, R. J.; Surg. Gynec. & Obst., **95:** 661, 1952.

TABLE 1

Per Cent Plasma	Clotting Times (Seconds)				
	H₂O	Normal saline	Cytal	Saturated boric acid	
					pH
100	(Clotting time, undiluted plasma 29 sec)				—
75	32	31	32	34	6 50
50	33	32	34	42	5 82
25	40	42	45	76	—
20	42	45	48	107	—
15	56	55	67	158	5 58
10	66	75	90	284	5 25

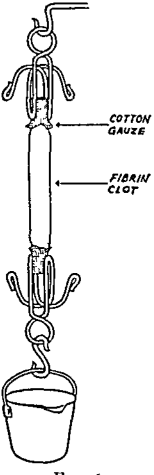

FIG 1

TABLE 2

Per Cent Clottable Fibrinogen	Diluent	Maximum Weight Supported in Grams		
0 54	Normal saline adjusted to pH 6 00	38	38	58
0 54	Saturated boric acid containing 0 15 M NaCl and adjusted to pH 6 00	43	43	43
0 50	Cytal containing 0 15 M NaCl and adjusted to pH 6 00	0	0	0

noted that all three solutions were adjusted to pH 6 00 and 0 15 M in sodium chloride This was necessary to obtain solution of the fibrinogen (Attempts to dissolve the fibrinogen in water and unmodified cytal or saturated boric acid were unsuccessful) The results are set forth in table 2

RESULTS AND CONCLUSIONS

From table 1 it can be seen that when the plasma is slightly diluted, the clotting time is approximately the same, regardless of which irrigating fluid is used as a diluent. This finding has a practical significance in that the undiluted or slightly diluted state approximates the conditions found in the immediate area of, or in the terminal lumen of, any bleeding vessel in the bladder wall or prostatic area. We would not, therefore, expect any one of the solutions to foster a hemorrhagic episode.

However, as the plasma becomes more diluted, there is an increase in the clotting times and a tendency to an increase in the increments in the clotting times between separate dilutions. It should be noted, furthermore, that in the higher dilutions this increase is greater with cytal and with the boric acid solution than with water or saline. In the case of boric acid solution, the large increase in clotting time is due to the low pH. This highly diluted state approximates the concentrations found in the bladder fluids at some distance from the bleeding site and suggests that with cytal or boric acid solution, the tendency of currents of blood to clot after leaving the bleeding point (i.e., in the vault of the bladder where clotting can do no good and much harm) should be much less.

The second experiment shows clearly that a fibrin clot, when formed in the presence of concentrated cytal, has negligible tensile or cohesive strength. As compared to saline or boric acid, this indicates that any fibrin blots which have formed and lie free in the bladder vault in the presence of concentrated cytal would, because of their friability, be quite unlikely to plug up the irrigating catheter postoperatively.

SUMMARY

Water, normal saline, saturated boric acid, and cytal have little effect on the clotting time of slightly diluted plasma. At the higher dilutions of plasma, however, the clotting times are greatest with cytal and saturated boric acid.

The tensile strength of clots formed in cytal is much lower than that of clots formed in saline or in saturated boric acid.

These results indicate a mechanism to explain the favorable clinical findings of Schulte, et al.[1] regarding the usefulness of cytal irrigations in concentrated form for the control of bladder clots. It is suggested that the decreased tendency to form firm clots even with the dilute cytal solution (also reported by Schulte's group) may be due to this same clot controlling mechanism.

ERRATA

February 1955 issue

p. 221: Legend for figure 2 should read: L, No. 50105, O.M.H. Tuberculous cystitis; incontinence. *A*, obstruction of ureter in solitary kidneys. *B*, nephrostomy.

p. 222: Legend for figure 3 should read: D. N., No. 282665, O.M.H. Inoperable carcinoma of bladder. *A*, dilatation of lower ureter of only functioning kidney. *B*, excretory urogram following ureterosigmoidostomy.

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VALUE AND LIMITATION OF ROENTGENOGRAPHIC DIAGNOSIS OF ADRENAL DISEASE

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Satisfactory roentgenograms of the adrenal glands are difficult to obtain because the glands are small structures adhering closely to the upper pole of the kidneys and their density to roentgen rays is approximately that of the surrounding retroperitoneal fat. Although large adrenal tumors characteristically cause renal displacement, many of the smaller tumors do not, and special techniques are required to demonstrate their presence roentgenographically.

It is the purpose of this paper to describe briefly the methods of roentgenographic visualization of the adrenal glands which we employ and to present our findings of the value and limitation of these methods in the diagnosis of various types of adrenal disease.

METHODS OF ROENTGENOGRAPHIC VISUALIZATION

In each patient with adrenal disease a *plain abdominal film* and *excretory urogram* are utilized first, a careful search being made for renal displacement and presence of soft-tissue masses in the suprarenal areas. For the 15-minute urographic roentgenogram, the patient is positioned so that the kidney and adrenal gland areas are centered on the upper third of the film, thus eliminating the need for retrograde pyelography in most instances.

When the urographic findings are normal, additional methods of roentgenographic examination are employed.

Presacral oxygen insufflation, which has recently gained popularity because of the introduction of a simplified technique,[1] frequently is utilized. The procedure involves the injection of oxygen into the presacral space from which it passes upward to the retroperitoneal space. Unfortunately, the procedure still has some drawbacks, namely, slight risk of gas embolism and discomfort to the patient and, occasionally, unsatisfactory contrast for visualization of the structures in the retroperitoneal area.

Translumbar aortography is utilized on a few occasions. It clearly demonstrates the blood supply of large adrenal tumors, but in our cases has proven of limited value in demonstrating small tumors or hyperplasia of the adrenal.

Laminagraphy (body-section roentgenography, planigraphy, stratigraphy, tomography, etc.), a method of roentgenographic projection of plane sections of solid objects,[2] is occasionally used. It is of practical value in demonstrating the adrenal glands and does not involve instrumentation or trauma to the patient.

In some patients surgical exploration of the areas of the adrenal gland is the

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Read at annual meeting, North Central Section of American Urological Association, Detroit, Mich., October 7–9, 1954.

[1] Rivas, M. R.: Am. J. Roentgenol., 64: 723–734, 1950.

[2] Andrews, J. R.: Am. J. Roentgenol., 36: 575–587, 1936.

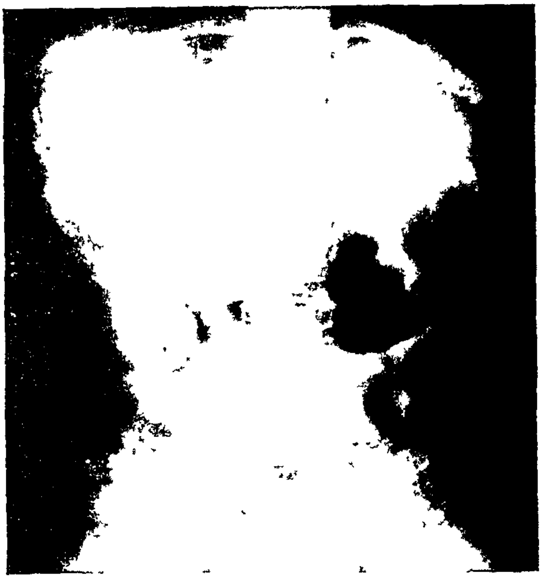

FIG. 1. Excretory urogram in a 9 year old boy, showing displacement of right kidney downwards by large adrenal tumor. Note stippled calcification characteristic of neuroblastoma (sympathogonioma).

only means by which the presence or absence of tumor can be definitely established.

ADRENAL DISEASES

Large nonhormonal adrenal tumors. Malignant medullary tumors of childhood known as sympathogoniomas or neuroblastomas, are readily visualized by intravenous urography because they cause renal displacement without much if any renal deformity or impairment of function. On excretory urography, five of 11 tumors of this type showed a characteristic stippled calcification in the tumor mass (fig. 1). Similarly, large, benign or malignant, nonfunctioning adrenal cortical tumors were demonstrated by intravenous urography in 13 patients. The differential diagnosis of nonhormonal adrenal tumors includes Wilms's tumor of the kidney, renal cell carcinoma, and primary, unattached, retroperitoneal tumors or cysts.

Pheochromocytoma. In the past 4 years, 5 patients have undergone surgery for removal of a pheochromocytoma. Four of the 5 patients with pheochromocytoma had normal intravenous urograms. Because most of these tumors were small, special techniques were required to demonstrate them roentgenographically. Only one of the 5 patients had an abnormal intravenous urogram (fig. 2); a soft-tissue mass above the right kidney caused renal displacement. That same patient had a small, nonfunctioning, cortical adenoma of the left adrenal gland which was not visualized by urography. Another one of the 5 patients had a pheochromocytoma, 6 cm. in diameter, which did not cause renal displacement demonstrable by urography (fig. 3). No special techniques were utilized to demonstrate the tumor. It was found only at laparotomy and was located directly in front of the upper pole of the left kidney.

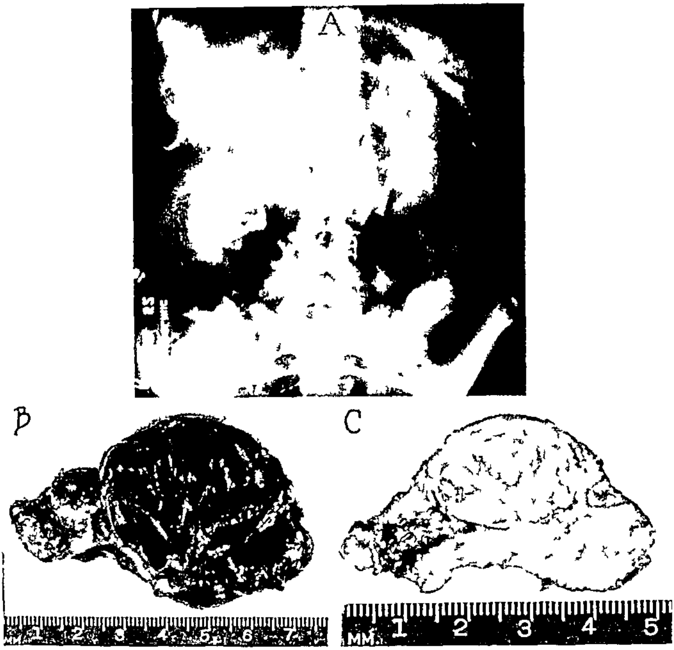

Fig 2 *A*, soft tissue mass in right adrenal gland with downward displacement of kidney shown by excretory urography Left kidney area appears normal *B* cystic pheochromocytoma of right adrenal gland *C* cortical adenoma of left adrenal gland of same patient

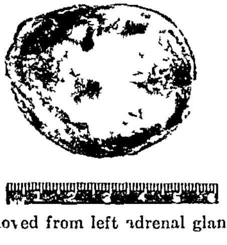

Fig 3 Tumor that was removed from left adrenal gland It was situated anterior to upper pole of kidney

In two instances, gas introduced into the retroperitoneal space outlined tumors which were not demonstrated by urography One of these patients was shown to have bilateral pheochromocytomas (fig 4) The tumor on the right was immediately above the kidney, the one on the opposite side lay anterior to the upper pole of the left kidney, and was visible only in the left oblique film

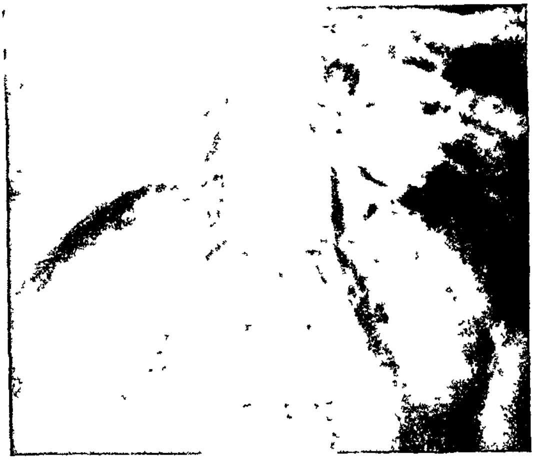

FIG. 6. Symmetrical adrenal glands shown by presacral oxygen insufflation in young woman with virilization due to adrenal hyperplasia.

riod of normal development may also be caused by adrenal tumor or hyperplasia. A more common cause of precocity in boys, however, is premature activation of the pituitary gland, stimulating the adrenals and gonads to produce somatic and sexual growth, known as constitutional premature puberty. Wilkins[5] has shown that patients with adrenal hyperplasia characteristically respond to administration of cortisone with reduction of their elevated 17-ketosteroid excretion, whereas those with adrenal tumor show no alteration in 17-ketosteroid excretion. However, further investigation of the response to cortisone is necessary.[6]

Roentgenographic visualization of the adrenal glands was utilized in patients with the adrenogenital syndrome when the evidence indicated the possibility of adrenal tumor. Nineteen patients with adrenogenital syndrome studied in the last 4 years had normal excretory urograms. Presacral oxygen insufflation was used in many of these patients (fig. 6) in an effort to demonstrate a tumor. Laminagraphy alone or in conjunction with insufflation was performed in 3 patients. In no instance was an adrenal tumor visualized nor have any patients with adrenogenital syndrome been shown later to have an adrenal tumor on the basis of their 17-ketosteroid assays while they were taking cortisone therapy. However, some of these patients are still being studied. Negative roentgenographic studies should not preclude surgery, however, when the diagnosis is definitely established on the basis of other findings.

Virilizing adrenal tumor of the adult male has never been recognized, but a few reports of males with feminizing tumors, of which the majority have been malignant, have been published.[7]

Cushing's syndrome: Overproduction of the adrenal corticosteroids which regulate carbohydrate metabolism produces a characteristic metabolic disorder known as Cushing's syndrome. It can be duplicated by the administration of large doses of cortisone or compound F. Cushing's syndrome can occur in childhood

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[5] Wilkins, L. and others: J. Clin. Endocrinol., **11**: 1–25, 1951.

[6] Venning, E. H., Pattee, C. J., McCall, F. and Browne, J. S. L.: J. Clin. Endocrinol., **12**: 1409–1425, 1952.

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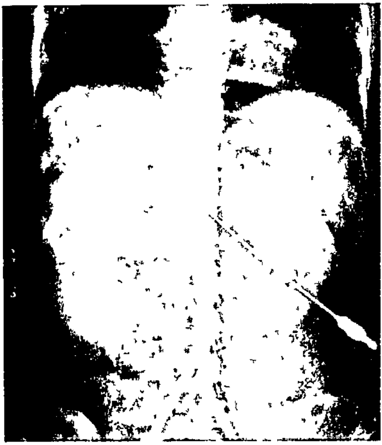

Fig. 7. Large, malignant, right adrenal tumor shown by translumbar aortography causing displacement of right kidney. Note metastases in both lung fields.

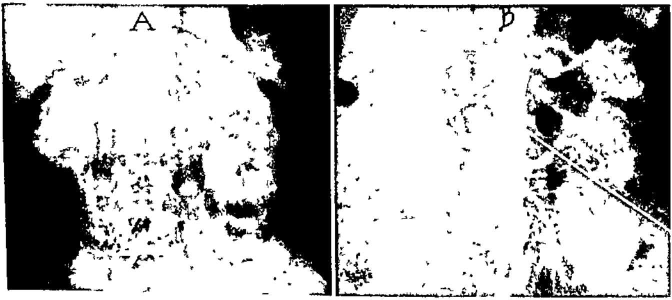

Fig. 8. *A*, small, soft-tissue mass above left kidney with downward renal displacement. *B*, translumbar aortogram showing excellent filling of splenic and renal arteries. Tumor lies just below aneurysmal dilatation of splenic artery. It shows no increased vascular markings.

or adult life and usually is caused by hyperplasia or tumor of the adrenal glands, although occasionally it can result from a basophilic pituitary tumor. During the past 4 years, 16 patients with this syndrome have been studied. One had a pituitary tumor, 11 had adrenal hyperplasia, and 4 had either a benign or a malignant adrenal tumor.

Roentgenographic study in these patients is important and should begin with a lateral view of the sella turcica for possible pituitary tumor, and intravenous urography. Renal displacement was demonstrated by urography in 3 patients, two of whom had a definite soft-tissue mass above the kidney. In each of these 2 cases, the tumor was malignant (fig. 7). The urogram of the third patient (fig. 8) showed downward displacement of the left kidney with the suggestion of a mass above the kidney, but findings on translumbar aortography were not diagnostic of tumor. An adenoma weighing 10 gm. was enucleated later from the left adrenal (fig. 9). Although it is widely known that aortography satisfactorily demonstrates the vascularity of a large adrenal tumor, it is of limited value in demonstrating small adenomas or hyperplastic glands.

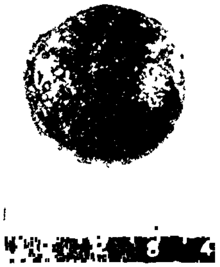

FIG. 9. Adenoma enucleated from left adrenal gland that had caused Cushing's syndrome

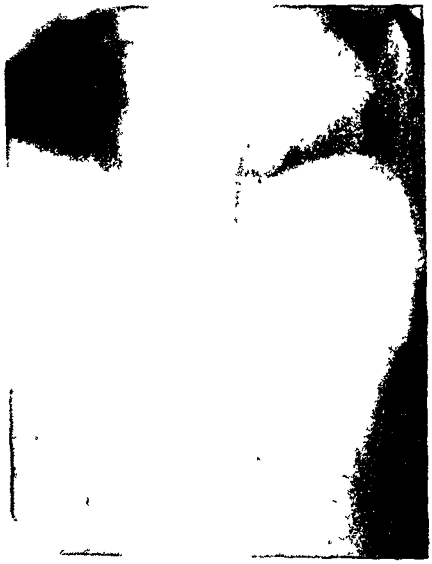

FIG. 10

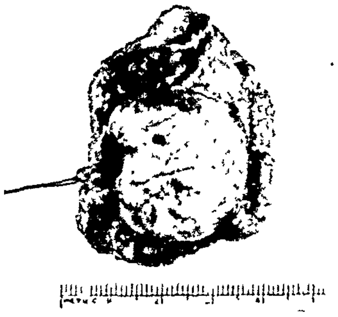

FIG. 11

FIG. 10. Small, triangular homogenous mass outlined overlying upper pole of left kidney by laminagraphy.

FIG. 11. Cortical adenoma of left adrenal gland which lay in front of left kidney. Ligature is around central adrenal vein.

One patient with Cushing's syndrome had a 7 cm. by 3.5 cm. adenoma of the left adrenal gland, with no evidence of renal displacement or soft-tissue mass on intravenous urography. Laminagraphy demonstrated (figs. 10 and 11) what was considered to be a soft-tissue mass just medial and anterior to the upper pole of the left kidney which at operation proved to be the exact location of the tumor.

The 11 other patients with Cushing's syndrome who had adrenal hyperplasia proven by operation all had essentially normal intravenous urograms. Three patients had presacral oxygen insufflation in addition, but findings were unsatisfac-

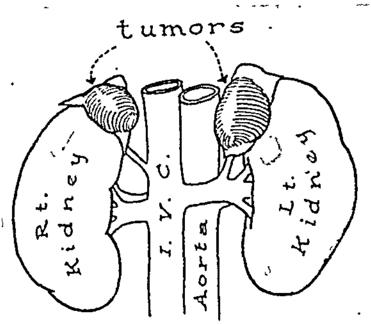

FIG. 12. Relationship of small adrenal tumors to kidneys. Left adrenal vein usually drains into left renal vein, right into vena cava. Roentgenographic visualization of small, left adrenal tumors is particularly difficult because they often lie anteriorly to kidney.

tory because in each case the gas did not fill the retroperitoneal space evenly on both sides although 1200 to 1800 cc of oxygen was utilized and the waiting period after insufflation was protracted. Increased fat deposition in the retroperitoneal space of patients with Cushing's syndrome may be a factor in preventing even distribution of the gas in the retroperitoneal space.

Calcification in the areas of the adrenal gland may represent healing from infection or hemorrhage, and may be found in some instances of Addison's disease. Calcification occasionally also occurs in tumors of the adrenal medulla or cortex,[8] and should not be ignored if the patient manifests other symptoms of adrenal disease.

DISCUSSION

The greatest value of roentgenographic visualization of the adrenal glands in patients with adrenal disease is the prospect of diagnosis of an adrenal tumor. Demonstration of an adrenal tumor permits selection of a suitable surgical approach depending on the size, location, and number of tumors. Visualization of normal or enlarged adrenal glands on both sides by special techniques may also be important in the differential diagnosis of growth problems in childhood or virilization of females, and under many circumstances makes laparotomy for adrenal tumor unnecessary.

Large adrenal tumors characteristically cause downward renal displacement with some degree of rotation of the upper pole of the kidney and the presence of a soft-tissue mass in the suprarenal region. These findings are usually evident on the intravenous urogram.[9] Small adrenal tumors seldom cause renal displacement and hence are often overlooked. For instance, of 6 small left adrenal tumors, ranging from 3 cm. to 7 cm. in diameter, only one caused displacement of the left kidney. It was one of the smallest tumors of the six, but it lay above the kidney and the central adrenal vein went directly into the vena cava. The other five tumors were mostly anterior and partly medial to the upper pole of the left kidney and in these, the central vein drained directly into the left renal vein (fig. 12). This is the more common situation in the left side,[10] and may explain why many small left adrenal tumors do not cause renal displacement. They can be demonstrated only by insufflation of gas, and with the use of oblique as well as anteroposterior roentgenograms, or by laminagraphy. In our experience both methods have proven successful in visualizing small adrenal tumors lying anteriorly to the left kidney.

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The adrenal gland on the right side is usually easier to demonstrate because it is more likely to lie just above the kidney. The main venous drainage usually is directly into the vena cava rather than into the renal vein. The liver, which ordinarily overlies the upper part of the right kidney, provides a uniform roentgenographic density; whereas on the left side, the fundus of the stomach often produces confusing shadows. Hence, the right adrenal gland stands out more clearly on insufflation of gas or on laminagraphy. The possibility of a tumor developing in aberrant adrenal tissue must always be considered, especially in patients with pheochromocytoma.[3] Negative roentgenographic findings in patients who are believed to have an adrenal tumor after careful endocrinologic study are not a contraindication to surgery, and laparotomy under such circumstances may be the only means by which the presence or absence of a tumor can be determined.

CONCLUSIONS

Excretory urography, presacral oxygen insufflation, laminagraphy, and aortography are briefly described as methods of roentgenographic demonstration of the adrenal glands. The value and limitation of each method in the diagnosis of various types of adrenal disease are discussed.

Visualization of an adrenal tumor is a valuable aid in the diagnosis and treatment of adrenal disease.

Endocrinologic methods of diagnosis of pheochromocytoma and of distinguishing the type of adrenal disease in patients with adrenal cortical hyperfunction are sufficiently reliable to justify laparotomy when the presence of an adrenal tumor is indicated, even though the tumor has not been visualized roentgenographically.

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METASTATIC ABSCESS OF PHEOCHROMOCYTOMA

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It is the purpose of this paper to report the first instance of a metastatic abscess within a pheochromocytoma of the adrenal gland. The abscess was apparently secondary to a bloodstream Salmonella infection. The patient's history indicates the probability that this septicemia followed a minor superficial face wound, which was contaminated by sewage.

A 29-year-old, white, married hardware salesman came to the Brooklyn Veterans Administration Hospital October 28, 1953. He complained of fever and chills of 3 weeks' duration. Prior to this illness he had enjoyed unusually good health. His past medical history included an appendectomy at the age of ten and an attack of Dengue fever in the Pacific Theater during World War II. For several years before the present illness he had had occasional attacks of "palpitation," which were not related to exertion.

Four weeks before admission, while cleaning a septic tank, the patient accidentally struck himself in the mouth with a shovel handle, sustaining a superficial abrasion.

Three weeks before admission there was an abrupt onset of fever and chills, the temperature reaching 102F. Fever, sweating, anorexia, and chills, with occasional rigors, continued until admission. Except for slight dysuria in the week before admission to the Veterans Administration Hospital, there were no other symptoms.

The patient was admitted to his community hospital October 16, 1953, and observed for 10 days. He was then transferred to a second private hospital, and thence in 2 days to the Brooklyn Veterans Administration Hospital. During these admissions no abnormal physical findings were detected. The laboratory studies in these private hospitals were thorough but inconclusive. The urine contained a trace of albumin and 20–25 pus cells per high power field. The white blood count ranged from 13,000 to 24,000, with 90 per cent polymorphonuclear leukocytes, and a shift to the left. The sedimentation rate was 35. Typhoid agglutination was positive in titres of 1:80 and 1:160. Paratyphoid B was positive in titres of 1:160 and 1:40. An excretory urogram showed an "enlarged left kidney." Blood smear for malaria, urine culture, blood culture, heterophil agglutination, and a chest film showed no abnormalities.

The patient was treated in these hospitals by penicillin and erythromycin, and experienced some subjective improvement. The fever, however, did not remit.

When he was admitted to the Veterans Administration Hospital on October 28, 1953, the temperature was 103F, pulse 90, respiration rate 24, and blood pressure 130/70. He was a well-developed man in no acute distress. The skin was dry

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Read at annual meeting, American Association of Genito-Urinary Surgeons, Shawnee-on-Delaware, Pa. May 26–28, 1954.

and flushed. The pharynx was reddened. A large herpetiform lesion was present on the lower lip, shotty lymph nodes in the right axilla and both groins, and a large varicocele in the left scrotum. All other physical findings were within the normal.

Extensive and frequent laboratory studies were made throughout the course of the illness. The urine was constantly within normal limits. The leukocyte count ranged from nine to eighteen thousand. The admission hemoglobin was 11 gm. Blood chemistry studies were all normal. All agglutination tests, except for the Salmonella typhimurium, were within normal limits. A blood specimen, drawn on the fourth hospital day, grew out a gram-negative rod of the Salmonella group, subsequently identified as Salmonella typhimurium. Cultures of the feces produced a growth of the same bacillus. Urine cultures were sterile. Sensitivity tests indicated that aureomycin and terramycin inhibited the growth of the isolated organism.

During November the patient received varying courses of aureomycin, terramycin and chloromycetin. There was flattening of the spiking temperature but a low grade fever continued throughout treatment. Transfusion with whole blood was necessary to correct anemia. In December, achromycin was tried, by mouth and intravenously, but without improvement.

In December, after excretory urography demonstrated a depression of the left kidney, cystoscopy was advised and performed. The bladder was found to be normal. Urine from each kidney, obtained by ureteral catheterization, was normal microscopically, and sterile by culture. Pyelograms showed vague psoas shadows, a slight scoliosis to the right, and depression of the left kidney by what the roentgenologist described as a "large, well-defined, globular mass, measuring 12 cm. in diameter." (See figure 1.) A double exposure of the abdomen showed that normal renal motion with respiration was present on both sides. Tomographic studies of the abdomen demonstrated the same round mass above the left kidney, but less distinctly.

Air insufflation studies were considered at this time, but were rejected because of the likely septic character of the mass. Since medical therapy was unavailing, and since there was an apparent mass above the left kidney, it was decided that surgical exploration should be attempted. The preoperative diagnosis was "left suprarenal tumor or abscess."

On January 15, 1954, under intratracheal cyclopropane anesthesia, the left loin was explored through the bed of the twelfth rib. Above a normal kidney, and replacing the adrenal gland, there was a firm, smooth, well-circumscribed mass, about the size of a small grapefruit. The mass was easily enucleated from the surrounding fatty tissue. Several large vessels, which supplied the tumor, were clamped, severed, and ligated with silk. During the manipulation of the tumor a marked elevation of blood pressure and pulse occurred. When the tumor had been excised a prompt precipitate drop in blood pressure followed. Regitine and norepinephrine were administered intravenously to regulate these fluctuations. The wound was closed in layers with black silk. One Penrose drain was inserted to the tumor bed.

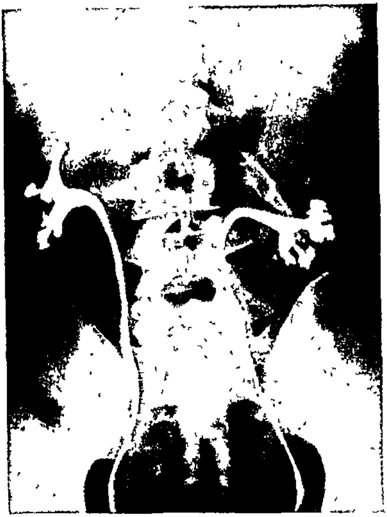

FIG. 1. Retrograde pyelogram demonstrating deviation of left kidney by suprarenal mass.

A stormy course followed the first 2 days. Norepinephrine in quantities sufficient to maintain normal blood pressure was given almost continuously for 36 hours. Cortisone was given prophylactically. Preoperative antibiotics were continued. On the second postoperative day the patient improved remarkably, and from that time made a speedy, uneventful recovery. He remained afebrile from the second day until his discharge 21 days after operation. All postoperative blood cultures were sterile.

The pathologist (Lester Fox, M.D.) described the specimen as follows: "An ovoid structure measuring 10 cm. in diameter. The surface is smooth with some adherent lobules of fat. On cut section it appears as a hollow sphere with a 1.6 cm. peripheral rim. The internal wall of the cyst is roughened and in folds with many projections. Microscopic examination reveals sheaths and interconnecting cords of purple polygonal and elliptical cells with central nuclei, abundant cytoplasm with granules and poorly defined cell border. Many of these cells are paler staining and appear degenerated. There are many foci of extravasated blood. There are several foci of lymphocytes and plasma cells. In some areas nerve cells are seen. Diagnosis: Pheochromocytoma; abscess formation; Salmonella typhimurium." See figures 2 and 3.

From the pus which the tumor contained, about 90 cc in volume, thick and yellowish, the Salmonella typhimurium was cultured.

The patient has remained in good health since discharge from the hospital. There has been no recurrence of fever. He has gained his normal weight. He has had no recurrence of the palpitation previously described.

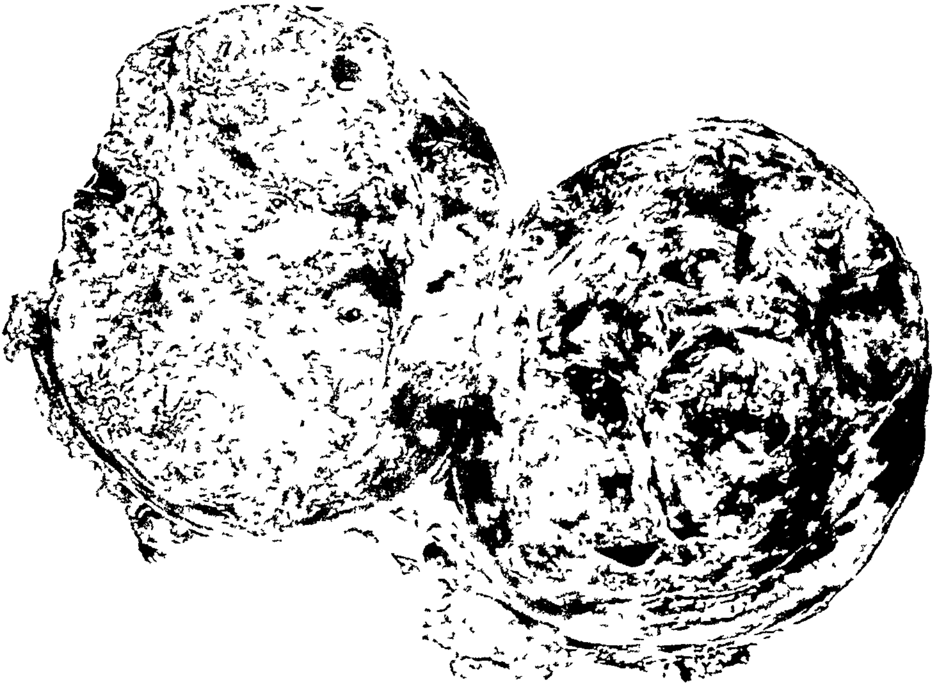

FIG 2 Bisected suprarenal mass. Light areas represent purulent material

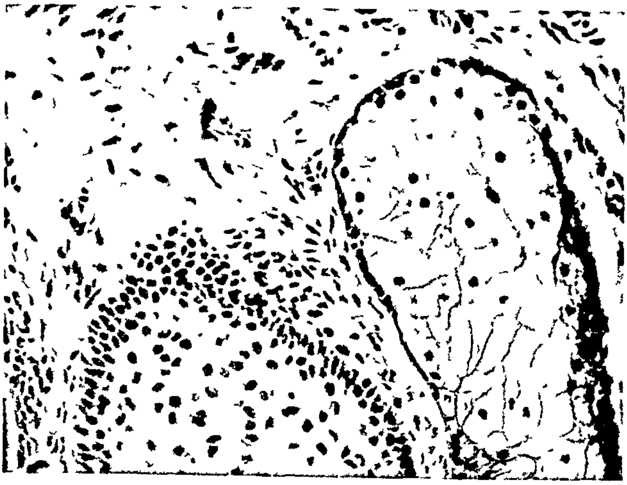

FIG 3 Photomicrograph Pheochromocytoma

DISCUSSION

Although cystic degeneration of a pheochromocytoma is almost a constant finding, and although many specimens are described as hemorrhagic and necrotic, no tumor has yet been reported in which there was an associated bacterial abscess. The case described in this report is believed to be the first of its kind.

Abscess from Salmonella typhimurium is not, however, a rarity. This organism is said by Dubos to be the most common cause of Salmonella gastroenteritis in the United States. The infection responds poorly to all drugs, but perhaps best to chloromycetin, and is very prone to relapse. The enteric infection has a usual course of about 3 weeks, and, when it persists beyond 6 weeks, a search for a localized source of re-infection should be diligently undertaken. In 3000 cases of Salmonella infection, Seligmann found 15 abscesses. The bones, the brain, old surgical scars, and the uterine cervical remnant have all harbored Salmonella abscess. The adrenal gland has never been reported as a site of Salmonella abscess.

A review of the facts in this case indicates that the patient had harbored a benign pheochromocytoma for several years. Then from a cesspool injury he was evidently inoculated with a systemic Salmonella infection, involving the gastrointestinal tract and the bloodstream. It can perhaps be assumed that the cystic necrotic center of the pheochromocytoma provided an opportunity for an abscess to develop, from which, in turn, the bloodstream was invaded. Both sites could, of course, account for persistent fever despite vigorous antibiotic therapy.

SUMMARY

A case of Salmonella typhimurium abscess with a symptom-producing pheochromocytoma of the adrenal is reported. It is concluded that this abscess was metastatic from a Salmonella septicemia. Diagnosis was inadequately established preoperatively but the patient was cured of both diseases by surgical excision of the abscessed tumor. A discussion of pheochromocytoma and Salmonella typhimurium abscesses is presented. This is believed to be the first reported instance of a bacterial abscess involving a pheochromocytoma.

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THE BLOOD SUPPLY OF THE NORMAL RENAL PELVIS*

ELMER DOUVILLE AND W. HENRY HOLLINSHEAD, PH.D.

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Although there have been numerous studies of the blood supply of other parts of the genito-urinary tract, there appears to be no detailed description of the vascular pattern of the renal pelvis. With the increasing number of surgical procedures that are being adapted to operations on the renal pelvis, more precise knowledge regarding its blood supply assumes added importance. A search of a number of standard anatomic texts of the United States and other countries, a number of specialized texts, and the original literature revealed only the rudimentary information that the renal pelvis receives its blood supply from the renal artery and, to quote one of the few descriptions (Smith and Copenhaver) that go beyond that, "The larger blood vessels run in the fibrous coat. From these, branches pierce the muscular layer, give rise to a capillary network among the muscle cells, and then pass to the mucosa. . . ."

We have therefore undertaken to investigate the origin, course and distribution of the arteries to the renal pelvis, with especial attention to the anastomoses which the vessels make with each other on the walls of the pelvis.

MATERIAL AND METHODS

Grossly normal human kidneys were obtained at necropsy from freshly embalmed bodies with no clinical history indicative of renal disease. They were perfused through the renal artery with isotonic saline solution, following which liquid latex or a combination of gelatin and India ink was injected (by syringe) into the artery. The renal pelves, major and minor calyces, and upper ends of the ureters were dissected free of the surrounding fat and renal parenchyma, the finer details of this dissection being carried out under a dissecting microscope, and the vascular pattern was studied under magnification. Of the 26 successfully injected specimens, ten were cleared and embedded in plastic for further study of details not visible in the opaque specimens.

OBSERVATIONS

Our dissections and preparations showed that the arterial blood supply of the renal pelvis originates from branches of the renal artery at several different levels (fig. 1), and consists of a large number of individually small vessels. Some of these vessels leave the renal artery or its branches outside the renal sinus and course through the perirenal fat, which they also supply, to reach the extrarenal portion of the renal pelvis. Others leave the anterior or posterior branches of the renal artery within the sinus, supply the peripelvic fat, and ramify on the upper part of the pelvis or on the major calyces. Still others, generally the smallest

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* Abridgment of thesis submitted by Dr. Douville to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Surgery.

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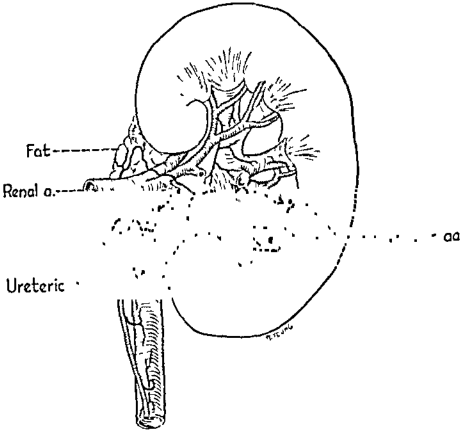

FIG. 1. Diagram of origins of arteries to renal pelvis. Anastomotic network which these vessels form in connective-tissue coat of pelvis is shown in photographs to follow.

but also the most numerous, are derived from the interlobar arteries as these leave the renal sinus to enter the parenchyma of the kidney, where they are close to the minor calyces. These branches descend along the minor calyces toward the major calyces.

The total number of arteries joining the minor calyces in any one kidney varied from 22 to 37. The minor calyces, in turn, numbered from five to nine, so that these calyces averaged about four vessels each. The pattern of the vessels on any minor calyx is essentially similar to that on any other minor calyx (fig. 2): they are slender vessels which course predominantly downward toward the major calyces but give off cross branches, sometimes as large as the main vessel, which anastomose with each other and with similar branches of the vessels close to them. On the major calyces they contribute to the network there.

The arteries to the renal pelvis from the peripelvic fat usually number from about four to seven, and are of relatively large size. As they or their branches reach the pelvis or a major calyx they branch and rebranch. These branches are directed longitudinally, transversely and obliquely along the pelvis or calyx. Two or three vessels usually end on the extrarenal portion of the pelvis, and branch as do those at a higher level.

All these arteries form a rich anastomotic pattern on the renal pelvis, major and minor calyces, and upper portion of the ureter (figs. 3, 4 and 5). Regardless of their source, they branch and anastomose freely in the loose connective-tissue coat adjacent to the muscular wall of the renal pelvis to form a relatively coarse plexus in the superficial part of this. Segments of many of these anastomosing vessels are extremely tortuous, even being wound into tight spirals, thus allowing for great expansion of the pelvis and calyces without tension on the blood vessels. The lowest vessels contributing to the vascular network of the pelvis are ascend-

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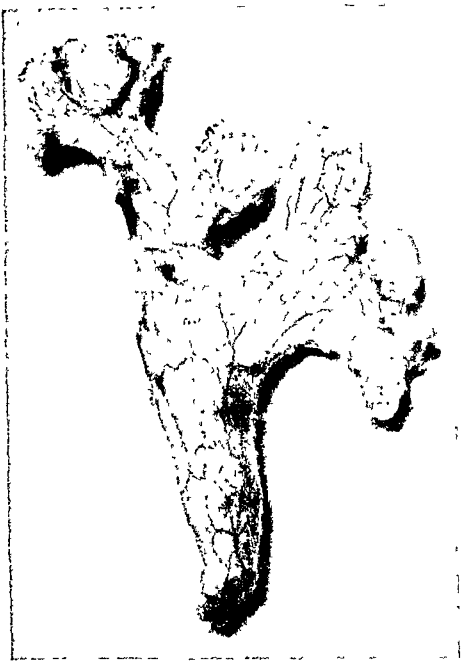

FIG. 4. Posterior surface of same specimen shown in figure 3.

ing branches from the upper ureteric artery (a derivative of the renal); the highest ones are the vessels, already described, that descend along the minor calyces. Clearing of the specimens emphasized that finer vessels derived from the coarser network form subsidiary plexuses in the deeper part of the connective-tissue coat. Vessels from these subsidiary plexuses penetrate the muscular coat to supply it and the mucosa; in the best-injected specimens a very rich plexus of fine vessels was seen in the mucosa.

Portions of the venous pattern could be recognized in many of the specimens in which the veins were not injected, and more detail was brought out in the four specimens in which the veins, either alone or in company with the arteries, had been injected. It was clear that the veins parallel the arteries in general, and, like them, anastomose freely with each other (fig. 5).

Although the specimens were selected at random, other than excluding those suspected of being diseased, from patients ranging in age from 18 to 86 years, no significant variations in the blood supply of the renal pelvis occurred among them. The one mildly hydronephrotic specimen that was available showed (fig. 5) a vascular pattern similar to that of the apparently normal pelves.

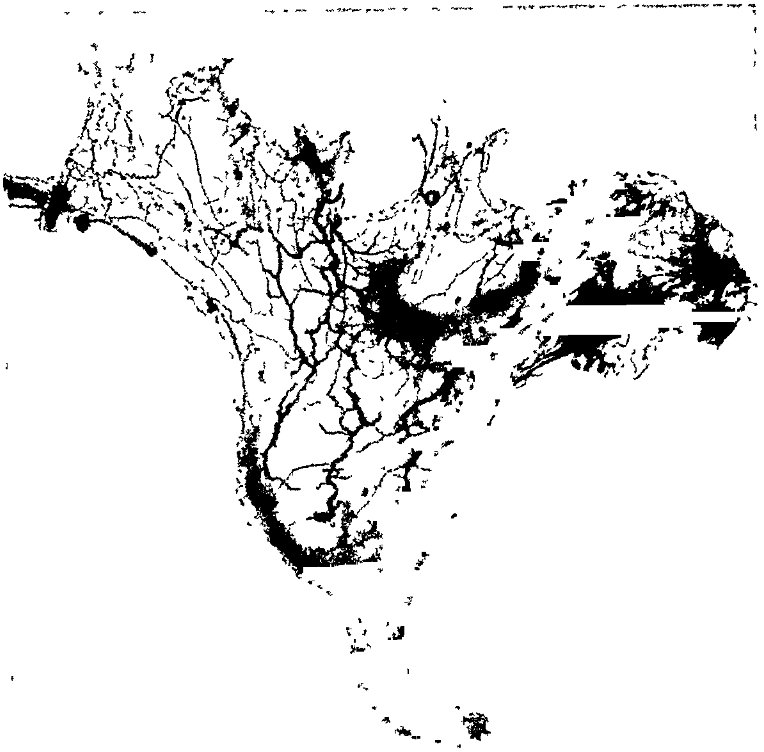

FIG. 5. Posterior view of mildly hydronephrotic specimen cleared and embedded in plastic after injection of arteries with gelatin and India ink, and of veins with blue latex. Arterial pattern here is partly hidden by veins; the latter, larger and blacker than arteries, are incompletely injected, but obviously form network similar to that of arteries.

COMMENT

The present study indicates that the normal renal pelvis has a blood supply so arranged that dangerous interference with it through surgical incisions appears very unlikely. Because of the multiple origin of the vessels reaching it, and the deep origin of the vessels that run along the minor calyces, the flow of blood to the renal pelvis can be completely eliminated only through occlusion of the renal artery itself.

In the connective-tissue coat the coarse network and its subsidiary ones are so arranged that it is impossible to determine, from anatomic observations, any prevailing direction of flow within them. It is true that relatively long and slender renal pelves tend to have the meshes of their coarser network somewhat elongated with the axis of the viscus, especially along the lower portion of the pelvis and on the major calyces, while short, wide pelves tend to have vascular networks in which the various diameters of the meshes are about equal; it is also true that not all the vessels entering into the network are of equal size, and hence some may be expected to supply more blood than others. However, the anastomoses between vessels entering the connective-tissue coat are so abundant and so relatively large that it is usually impossible to follow a contributing channel for any distance—it commonly loses its identity in the network. Also, the anastomotic branches between two vessels commonly undergo no perceptible diminution in caliber, so that it is impossible to judge at what point vessels of different origin merge. The nature of the network and the fact that it is formed by numerous vessels that leave the renal artery at different levels and reach the renal pelvis from all directions and at all levels make it difficult to imagine a surgical incision that would devascularize a part of it.

While the blood supply of the renal pelvis and that of the ureter are similar in certain respects, the differences are more important than the similarities. In both, the blood supply is multiple, and the entering vessels form plexuses in the connective-tissue coat; however, the vessels to the renal pelvis are far more numerous than are those to the ureter, which commonly has only two to four grossly visible ones; moreover, the vessels of the pelvis reach it so close together that every part of the vascular network is formed by anastomosing branches of several stem arteries, while the few vessels of the elongated ureter necessarily reach that structure at considerable distances from each other, and the vascular network on each side of the point of entrance of a stem vessel is derived exclusively from that vessel—in consequence, collateral circulation to a segment of ureter is dependent on the anastomoses that successive vascular networks make with each other. Daniel and Shackman concluded that in some 10 to 15 per cent of ureters the anastomoses between consecutive entering vessels of the ureter are inadequate, so that while some ureters can safely be divided anywhere, a minor number will undergo necrosis if sectioned more than about 2 cm. below the level of entrance of a visible entering vessel. In spite of the similarities, therefore, the blood supply of the renal pelvis is in sharp contrast to that of the ureter.

Similar investigation of the pelvic blood supply of kidneys with various degrees of hydronephrosis has been planned for a subsequent report. We were unable to detect any differences in the vascular pattern of the slightly hydronephrotic pelvis that we examined during the current study.

SUMMARY

A study of 26 specimens of the renal pelvis, major and minor calyces, and upper portion of the ureter showed a constant rich arterial and venous anastomotic blood supply. The arterial blood supply originates from the renal artery at several levels: some branches course through the perirenal fat to reach the extrarenal portion of the pelvis, where they are joined by branches ascending from the upper end of the ureter; others leave the branches of the renal artery within the renal sinus and course through the peripelvic fat to the upper part of the pelvis and to the major calyces; and numerous ones, taking origin from the interlobar arteries as these enter the renal parenchyma, run along the minor calyces toward the major ones.

In the loose connective-tissue coat of the pelvis and major calyces the contributing arteries quickly lose their identities as they branch and anastomose freely with each other in a relatively coarse network. From this are derived finer

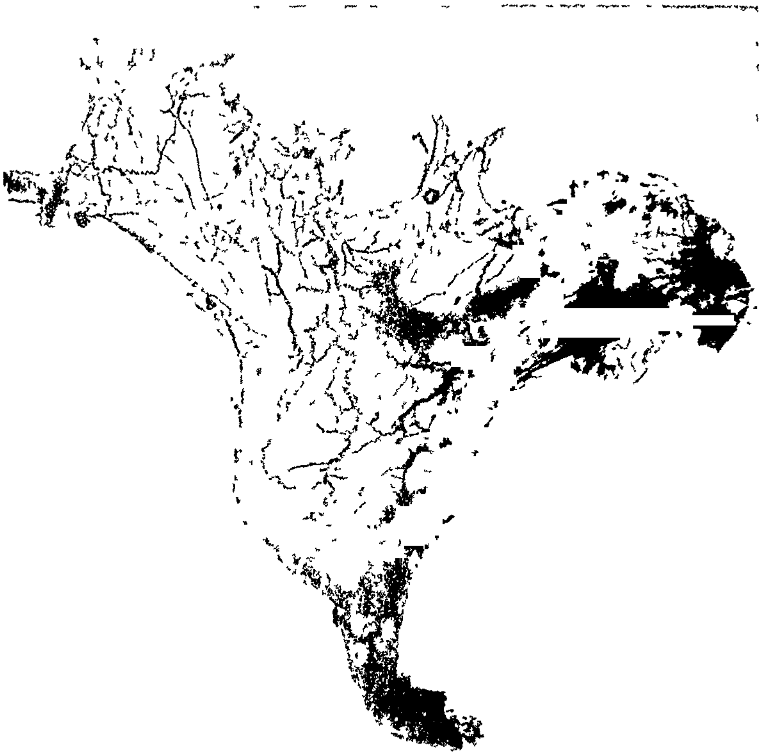

FIG. 5. Posterior view of mildly hydronephrotic specimen cleared and embedded in plastic after injection of arteries with gelatin and India ink, and of veins with blue latex. Arterial pattern here is partly hidden by veins; the latter, larger and blacker than arteries, are incompletely injected, but obviously form network similar to that of arteries

COMMENT

The present study indicates that the normal renal pelvis has a blood supply so arranged that dangerous interference with it through surgical incisions appears very unlikely. Because of the multiple origin of the vessels reaching it, and the deep origin of the vessels that run along the minor calyces, the flow of blood to the renal pelvis can be completely eliminated only through occlusion of the renal artery itself.

In the connective-tissue coat the coarse network and its subsidiary ones are so arranged that it is impossible to determine, from anatomic observations, any prevailing direction of flow within them. It is true that relatively long and slender renal pelves tend to have the meshes of their coarser network somewhat elongated with the axis of the viscus, especially along the lower portion of the pelvis and on the major calyces, while short, wide pelves tend to have vascular networks in which the various diameters of the meshes are about equal; it is also true that not all the vessels entering into the network are of equal size, and hence some may be expected to supply more blood than others. However, the anastomoses between vessels entering the connective-tissue coat are so abundant and so relatively large that it is usually impossible to follow a contributing

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THE TREATMENT OF ACUTE TRAUMATIC RENAL INSUFFICIENCY

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The clinical management of acute renal insufficiency has improved in the past 5 years, through the efforts of research teams devoting their efforts to solving the many problems, and the constant physiological research relating to electolytes. The recent Korean War presented the research team from Walter Reed Hospital[1] with numerous cases of lower nephron nephrosis. This paper will seek to correlate some of the facts learned while working with this group and observing the treatment of more than fifty of these cases, plus a limited experience gained in private practice. The results obtained by the research team will be published by Major William Meroney, of the Army Medical Service Graduate School.

The syndrome of lower nephron nephrosis was probably first described by Minami.[2] But it was not until Bywaters and Beall[3] in 1941, and Lucké[4] in 1946, described the syndrome that the medical world awakened to its full importance. I believe that the term "acute tubular nephrosis" as proposed by Moon[5] more accurately describes the pathological picture; however, the term "lower nephron nephrosis" has entered our medical language and will probably remain.

PATHOLOGY

As the name "lower nephron nephrosis" implies, it was first thought that the principal pathological lesion was limited to the distal convoluted tubules. Oliver,[6] however, showed that this was not the case. He dissected entire nephrons from involved kidneys and demonstrated that there were disseminated areas of epithelial degeneration and necrosis and/or rupture of the basement membrane, neither of which was predominant in the distal part of the nephron.

The gross appearance of these kidneys is not characteristic. The kidney is usually slightly enlarged, swollen, and may have a pale appearance. The capsule is not adherent and the underlying parenchyma may show evidences of recent hemorrhage. Microscopically the glomeruli usually appear normal but some believe that, even here, there are consistent changes in the vascularity of the tuft and the basement membrane (French[7]). In the proximal portion of

Accepted for publication July 21, 1954.

[1] Surgical Research Team, Army Medical Service Graduate School, Walter Reed Hospital, Washington, D. C.

[2] Minami, S.: Ueber nierenveranderungen nach Verschuttung. Virch. Arch. f. Anat., 245: 247–267, 1923.

[3] Bywaters, E. G. L. and Beall, D.: Crush injuries with impairment of renal function. Brit. M. J., 1: 427, 1941.

[4] Lucké, B.: Lower nephron nephrosis. Mil. Surg., 99: 371–396, 1946.

[5] Moon, V. H.: Acute tubular nephrosis, a complication of shock. Ann. Int. Med., 39: 51–60, 1953.

[6] Oliver, J., MacDowell, M. and Tracy, A.: The pathogenesis of acute renal failure associated with traumatic and toxic injury: Renal ischemia, nephrotoxic damage, and the ischemuric episode. J. Clin. Invest., 30: 1307–1438, 1951.

[7] French, A. J.: Glomerulonephrosis: A morphologic manifestation of renal cortical ischemia in toxic oliguria and lower nephron nephrosis. Arch. Path., 49: 34–54, 1950.

the nephron the epithelial cells usually show some degree of cloudy swelling but may be necrotic. The descending loop of Henle as a rule appears normal but may show a degree of cloudy swelling. In the ascending loop of Henle and distal convoluted tubule the distinctive features are areas of necrosis and epithelial regeneration, depending upon the duration of the syndrome. In the distal convoluted tubules and collecting tubules hyaline or pigment casts can be seen, depending upon the etiology.

ETIOLOGY

No less than fifty different causes have been enumerated for this syndrome. These may be grouped under the following headings: 1) prolonged shock from any cause; 2) trauma; 3) hemoglobinemia; 4) toxins, bacterial or chemical; 5) sensitization reactions; 6) radiation; 7) anoxemia.

It was my observation that those cases in which acute tubular nephrosis developed secondary to severe battle injuries and multiple transfusions (average colloid replacement required per patient, 6000 cc) were no more severely wounded (muscle damage and shock, etc.) than other patients who did not have acute tubular nephrosis. Possibly those patients who did not have acute tubular nephrosis had a greater glomerular filtration volume per minute during their period of shock than those who developed renal insufficiency. This may have prevented the formation of hemoglobin or myohemoglobin casts, which may in turn be one of the pathological causes of oliguria. Oliver[8] believes that the importance of tubular casts, acting as "plugs" in the tubular system, has not been appreciated in the causation of oliguria. The thought occurs to one that, adding an osmotic diuretic to Red Cross blood, e.g., sorbitol or mannitol, might maintain a higher filtration rate per minute in the kidneys of these severely wounded patients and, perhaps, prevent or minimize the development of acute renal insufficiency.The "plugging" effect of casts probably applies only to a small percentage of cases of oliguria. In battle injuries, however, where large amounts of type O blood are used, I believe the incidence of hemoglobinemia and resulting cast formation is much higher. Hence, it would seem logical to try to prevent this group of anurias by adding an osmotic diuretic to the blood used by the military services.

CLINICAL COURSE

The clinical course of acute tubular nephrosis is fairly uniform regardless of the numerous causes, because of the time necessary for the kidney to regenerate from the insult causing the syndrome. Swann and Merrill[9] have recently given an excellent discussion of this syndrome.

Oliguric phase. This is the period of reduced urinary output, in which the volume is less than 400 cc/day. It comes on immediately after the injury and lasts a variable period, ranging from a few days to several weeks. The average duration of this phase, as found by the Army Research Team[1] was 9½ days. During the period of oliguria the patient's blood pressure starts to rise about the third to fifth day and the danger of coma and/or convulsions presents itself. The cerebral signs are probably due to cerebral edema secondary to overhydration, electrolyte imbalance, hypertensive encephalopathy, and uremia.

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[8] Oliver, J.: New directions in renal morphology: A method, its results and its future. Harvey Lect., **40:** 102, 1944–45.

[9] Swann, R. C. and Merrill, J. P.: The clinical course of acute renal failure. Med., **32:** 215–292, 1953.

The period of oliguria, in addition to electrolyte and nonprotein nitrogen imbalance, is marked by poor wound healing and anemia. Finch[10] showed that there was a delay in the uptake of Fe in renal disease. The factors of increased hemolysis and toxic depression of bone marrow from associated infections also contribute to the degree of anemia. The anemia, the marked catabolism, and the poor protein intake during the period of oliguria probably account for the poor wound healing.

During the oliguric phase there may be gastrointestinal symptoms such as nausea, vomiting, and possibly diarrhea. Severe gastrointestinal bleeding may develop with higher levels of uremia.

Diuretic phase. The oliguric phase is followed by the diuretic phase, in which the urine volume is greater than 500 cc per day. It is during this phase that the selective absorption of the tubules is faulty and there is a marked loss of sodium, potassium, and bicarbonate ions. This salt wastage by the kidneys may continue for weeks or months, so that these electrolytes must be watched carefully and replaced. Interestingly enough, the nonprotein nitrogen remains elevated even though the urinary output is high. Probably this is due to increased tubular absorption during the period of recovery. Whatever the cause the nonprotein nitrogen does not return to normal limits for several weeks following the onset of diuresis.

During the first 7 to 10 days of the syndrome the principal causes of death are pulmonary edema due to overhydration, and cardiac arrest secondary to hyperkalemia. In the diuretic phase the principal causes of death are overwhelming infection and electrolyte imbalance.

DIFFERENTIAL DIAGNOSIS

Acute tubular nephrosis must be differentiated from oliguria secondary to dehydration; primary renal disease, much as acute glomerulonephritis, acute pyelonephritis, or acute exacerbations of chronic glomerulonephritis; bilateral ureteral obstruction secondary to calculi, sulfa crystals, or metastatic carcinoma; and renal vascular lesions much as venous or arterial thrombosis.

TREATMENT

General. After the syndrome of acute tubular nephrosis has been recognized, immediate steps should be taken to control the cause, whatever that may be. An accurate history of the intake and the output must be obtained to determine the amount of overhydration present and to help the regulation of the fluid balance. Of course an accurate intake and output chart must be maintained throughout the entire treatment. It is important to insert a retention catheter for more accurate measurements, the bladder being irrigated daily with a measured amount of 1:2000 zephiran solution in order to keep the catheter patent.

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[10] Finch, C. A., Sawyer, C. G., Peacock, W. C. and Fluharty, R. G.: Iron metabolism, utilization of IV radioactive Fe. Blood, 4: 905, 1949.

An electrocardiogram should be taken as soon as possible to serve as a basis for future comparison, as this is a sensitive means of evaluating hyperkalemia. A daily electrocardiogram should be taken thereafter to observe the effects of hyperkalemia and/or cardiac insufficiency. As the plasma level of potassium rises it will be necessary to take electrocardiograms more often in order to determine the rapidity and degree of potassium intoxication. Meroney and Herndon[11] point out that the degree of potassium may be much greater than the plasma level of potassium would indicate, if there is hypocalcemia, secondary to the hyperphosphatemia produced by the renal insufficiency. This is the basis for the treatment of the acute hyperkalemic emergency with calcium gluconate.

Daily determinations of plasma potassium, sodium, chlorides, phosphates, calcium, complete blood count, CO_2 combining power, and hematocrit are essential to the proper handling of the electrolyte and fluid balance. The patient should be weighed daily to determine the degree of catabolism and overhydration. If possible, a daily blood culture should be taken. If the culture is positive, then antibiotic sensitivity tests should be run on the organisms to determine the most effective antibiotic.

Cardiac and cerebral complications. The reader is referred to Hopper,[12] Murphy,[13] Swann,[9] Corcoran[14] and Iseri[15] for the treatment of cardiac failure and the cerebral complications occurring during the course of acute tubular nephrosis. It should be emphasized that a convulsion liberates a large amount of potassium into the plasma. With hyperkalemia prior to the convulsion, a sudden plasma increase of potassium may be fatal.

Fluids and caloric intake. I believe that a more accurate knowledge of fluid and caloric intake can be determined if the intravenous route only is used. By deleting oral feedings one can prevent the absorption of any additional potassium which may be in the diet. A slow, continuous drip through a venous cannula of polyethylene tubing serves as an excellent method of administering fluids, electrolytes, glucose, and medications.

Knowing the pathological lesions in the kidneys and the ever present danger of pulmonary edema, the intake of water should be kept at an absolute minimum. Practically all of these patients are overhydrated and hence it is unwise and unnecessary to replace all of the daily insensible loss of water. The amount of water to be administered can be calculated by adding 250–400 cc (⅓ to ½ of the estimated daily insensible loss) to the volume of urinary output, the estimated amount of water in the stools, and the amount of water obtained from gastric suction and/or vomiting. To this small amount of water (500–750 cc) must be added all the necessary calories, electrolytes, and medications needed to sustain the body. Thus, it is necessary to use hypertonic solutions of glucose and electrolytes. Meroney[1] used 25 per cent glucose solution, 3 per cent sodium chloride solution, and 7½ per cent sodium bicarbonate solution. Golden[16] has shown that hypertonic glucose solutions may cause a glucose nephrosis. Possibly a hypertonic solution of fructose, which is metabolized more readily than glucose, or a hypertonic fructose and neutral fat solution would be best for its protein sparing effect.

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[11] Meroney, W. H. and Herndon, R. F.: Ionic interrelationships and potassium intoxicacion. To be published.

[12] Hopper, J., O'Connell, B. P. and Fluss, H. R.: Serum potassium patterns. Ann. Int. Med., **38:** 935–954, 1953.

[13] Murphy, F. D.: Acute toxic nephrosis. Postgrad Med., **12:** 191–200, 1952.

[14] Corcoran, A. C.: Advances in treatment of acute and chronic renal insufficiency. J.A.M.A., **153:** 1233–1236, 1953.

[15] Iseri, L. T., Batchelor, T. M., Boyle, A. J. and Myers, G. B.: Studies of fluid, electrolyte, and nitrogen balance in acute renal insufficiency. A.M.A. Arch. Int. Med., **89:** 188–215, 1952.

To the hypertonic carbohydrate solution one unit of insulin should be added for every 2 gm. of carbohydrate. The insulin facilitates the metabolism of the glucose; in its catabolic phase of supplying calories and in its anabolic phase where glucose is laid down within the cell as glycogen. During the deposition of the glycogen within the cell, potassium is pulled intracellularly. Vitamin B_1, C, and K should be added to the intravenous fluids.

It is necessary to give at least 250 cc of whole blood daily, and often more. This is to control the anemia and restore depleted proteins. It is given independent of the other fluids and does not enter into the calculations for fluid replacement.

Surgical considerations. In those cases of acute tubular nephrosis that have sustained injury either as a result of battle injuries or surgery, it is extremely important that the wounds be kept clean of necrotic tissue. When it is realized that the intracellular potassium concentration varies from 95 to 125 mEq/L[17] then one can appreciate the amount of potassium that can be absorbed from the disintegrating cells. This also applies to hematomas, abscesses, and to any infection in which bacteria liberate necrotizing and hemolyzing toxins. It is imperative that all wounds be kept scrupulously debrided, and abscesses or hematomas be evacuated of their contents. In fact, one can often tell by the rapid deterioration of the electrocardiogram or a sudden rise in the plasma potassium level that either the wounds have not been adequately debrided or that some hematoma or abscess has been overlooked.

Treatment of hyperkalemia. The control of hyperkalemia is one of the biggest problems in treating these patients. Since there is no way of eliminating the excess potassium derived from the increased catabolism, then advantage must be taken of physiological and pharmacological antagonists, as well as dialysis, if necessary.

As has already been mentioned, 75–100 mEq/L of potassium are usually taken into the body from protein in the food. By using intravenous carbohydrates and fats this danger can be lessened. However, as Corcoran[14] points out, one day's fast releases 140 mEq/L of potassium from the catabolism of 70 gm. of protein. Therefore, it is most essential that as full caloric carbohydrate and fat intravenous maintenance be provided, as possible.

Calcium is a pharmacological antagonist of potassium[11] in that the toxic effects of potassium are accentuated by hypocalcemia (usually present with the hyperphosphatemia of renal insufficiency) while the toxic effects of a high plasma potassium can be alleviated temporarily, by calcium gluconate intravenously.[11, 17, 18] However the effects of ionic calcium in a continuous intravenous drip are of relatively short duration, 2 to 12 hours, so that the procedure should be used only in emergencies. It should also be mentioned that a second course of calcium, to control the effects of hyperkalemia, is not so effective as the first. In regard to the amount of calcium gluconate needed to reverse the toxic effects of potassium, this can only be ascertained by watching the effects on the electrocardiogram, as it may require 5 to 15 gm. or more to overcome the toxic effects.

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[16] Golden, K. F. and Prior, J. T.: Glucose nephrosis with renal failure in a patient with Laennacs cirrhosis. Ann. Int. Med., **39:** 1308–1315, 1953.

[17] Nadler, C. S.: Recent advances in potassium metabolism. Am. J. Med. Sci., **226:** 88–103, 1953.

A more effective ion in controlling hyperkalemia is sodium. Most authors writing on the subject mention the striking tendency for sodium to fall. Iseri[15] believes that this is due to the administration of disproportionately greater amounts of water than electolytes, to greater cellular uptake of sodium, to the shift of water from cells to extracellular fluid, and to the loss of electolytes through other channels. One important cause that he fails to mention is the reluctance of the physician to give sodium ion to the oliguric patient in the mistaken belief that it will cause pulmonary edema, while actually it is the overhydration that is the cause of the pulmonary edema and not the hypernatremia. One other mechanism which has not received too much consideration is the ion shift that occurs with changes in the pH of the extracellular fluid (ECF). Keating[19] showed in the nephrectomized dog that when the pH of the ECF was decreased by saline or ammonium chloride infusions, the potassium in the ECF actually increased, thereby proving that acidosis causes a shift of potassium out of the cell and sodium shifted into the cell. However, when the pH of the ECF was raised by sodium bicarbonate solution there was an actual decrease in the amount of extracellular potassium. Therefore, since the end products of catabolism are acid, and there is no way for the body to excrete the accumulating acid radicals, acidosis develops,[12] and the sodium ion migrates intracellularly at the same time, displacing some potassium ions into the ECF.

There is probably a great deal of sodium lost from the extracellular fluid into hematomas and areas of inflammation by osmotic diffusion into these areas of high potassium concentration.

It follows that it is of great importance to maintain the plasma sodium as near normal (or slightly above normal) as possible in order to prevent acidosis and the resulting potassium shift to the ECF. Clinical evaluation has shown this to be true. There is no danger of pulmonary edema as long as the water intake is restricted. Numerous cases showed a marked fall in plasma potassium when the plasma sodium was brought up to normal or to higher than normal values. The sodium is best given in the form of sodium bicarbonate or sodium lactate, unless the chlorides are markedly low.

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[18] Merrill, J. P., Levine, H. D., Somerville, W. and Smith, S. III: Clinical recognition and treatment of acute potassium intoxication. Ann. Int. Med., **33**: 797, 1950.

[19] Keating, R. E., Weichselbaum, T. E., Alanis, M., Margraf, H. W. and Elman, R.: The movement of potassium during experimental acidosis and alkalosis in the nephrectomized dog. Surg., Gynec. & Obst., **96**: 323–330, 1953.

Another conservative measure that can be used to decrease the plasma potassium is to initiate diarrhea in the patient with some nonelectrolyte cathartic There is a large amount of potassium lost in the fecal contents This, of course, requires that careful and frequent plasma electrolyte levels be run in order to replace the necessary sodium and chlorides lost, as well as volume for volume water replacement

The specific exchange resins, e g SKF No 648, are of definite value in removing potassium by osmotic exchange However, in the complicated critically wounded cases, with renal insufficiency, the catabolism is so great that these resins can not keep up with the liberation of potassium into the ECF But in the cases seen in civilian practice they will be of definite value They are probably best used rectally as this method gives the physician more control over the absorption of water and sodium, by limiting the amount of time the resins are allowed to remain in the lower colon

Of course the most effective method of treating hyperkalemia and uremia is by dialysis This method has gradually evolved as an important adjunct to the treatment for these patients but should only be used if the clinical management has gotten out of hand or to eliminate the effects of uremia In those cases resulting from battle injuries, where there has been large amounts of tissue damage, the "artificial kidney" is much more important This is due to the greater amounts of potassium liberated by the necrotic tissue and the increased rate of increase of the nonprotein nitrogen The results of the use of dialysis by the research team in Korea will be published by the Army Research Team [1] Merrill[9, 20] has given an excellent review of the uses and the indications for the artificial kidney in civilian practice

SUMMARY

The syndrome of acute renal insufficiency may be induced by multiple causes which may be classified simply as follows 1) prolonged shock from any cause, 2) trauma, 3) hemoglobinemia, 4) toxins, bacterial or chemical, 5) sensitization reactions, 6) radiation, 7) anoxemia

Whatever the cause, the pathological picture and clinical course are essentially the same Pathologically there is cloudy swelling and necrosis of the nephron, with the most marked changes in the tubular system There is precipitation of myohemoglobin, hemoglobin, and other proteins within the tubules, probably producing a mechanical blockage to the flow of urine The clinical course consists of the oliguric phase lasting about 10 days, and the diuretic phase which extends over several weeks During the former there are profound metabolic changes 1) elevation of nonprotein nitrogen, 2) acidosis, 3) hyperphosphatemia and reciprocal hypocalcemia, 4) accumulation of toxic metabolites, not well defined, and 5) most important, hyperkalemia

The mechanism of hyperkalemia deserves emphasis because of its dire effects and the special efforts required to combat it Sources of the increased potassium

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[20] Merrill J P The use of the artificial kidney in the treatment of uremia Bull New York Acad Med, 28 523-531 1952

in the blood are: 1) tissue breakdown from extensive wounds, infections, and hematomas, 2) catabolic mechanisms incident to diminished caloric intake, 3) acidosis with the resulting ionic shift of potassium from the cells to the extracellular fluid.

The diuretic phase is characterized by electolyte depletion and, therefore, continued vigilance is necessary. The nonprotein nitrogen remains high for a long time. These unusual changes are no doubt due to faulty absorptive mechanisms in the regenerating epithelium.

Death, when it does not occur from associated wounds or overwhelming infections, usually occurs from pulmonary edema due to overhydration or cardiac arrest secondary to hyperkalemia.

The principles of treatment are: 1) careful regulation of fluid intake, with particular care not to overwhelm the patient with fluid that cannot be excreted; 2) regulation of acid-base balance; 3) maintenance of caloric intake; 4) small frequent blood transfusions to control anemia and restore depleted proteins; 5) antibiotics and vitamins; 6) dialysis, by means of the artificial kidney in severe cases; and 7) the control of hyperkalemia. Emphasis is placed upon the use of electrolyte antagonists to potassium, and particularly the use of adequate amounts of sodium.

The use of an osmotic diuretic, such as sorbitol or mannitol, is suggested in Red Cross blood, as a means of maintaining glomerular filtration during the first critical hours of shock following injury, and thereby possibly preventing the mechanical blocking of tubules by precipitated proteins.

The care of these patients is difficult, tedious, and trying in the extreme. But it should ever be kept in mind that once over the critical oliguric phase, the kidney will probably be restored entirely to normal. This wonderful regenerative capacity justifies all efforts. The rewards are great.

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TREATMENT OF ACUTE UREMIA

WALTER A. KEITZER

When oliguria or anuria is present for several days, the resultant renal insufficiency is reflected in the chemical blood tests as an increase of the nitrogen, phosphorus, potassium and acids; and as a decrease in the sodium chloride, calcium, CO_2 combining power and red blood count. During this early period, the patient is usually able to take fluids, food and feels fairly well. This is called the pre-uremic phase. After 4 to 7 days of acute renal insufficiency, a clinical syndrome occurs called acute uremia.[1] This uremic phase is recognized by mental confusion, marked abdominal distention, continuous vomiting, hiccups and jerking of the extremities. How rapidly the patient changes from the pre-uremic to the uremic phase depends upon how well the patient has been treated. The diuretic phase may begin any day after the onset of anuria up to the thirty-first day provided that the patient will live that long. This final phase represents regeneration of the kidneys. From the standpoint of therapy, it is convenient to classify the etiologic agents in three major groups: 1) obstructive uropathies; 2) fluid and electrolyte imbalances; 3) intrinsic renal lesions.

ACUTE UREMIA SECONDARY TO OBSTRUCTIVE UROPATHIES

Obstructive lesions of the urinary tract may occur anywhere from a stricture of the urethral meatus to blockage of the renal collecting tubules by sulfa or uric acid crystals.* A good history of the patient, plus a cystoscopy and retrograde pyelogram will make the diagnosis as well as cure many of these patients. A few case reports will illustrate the usual conditions seen in the practice of urology.

Case 1. C. C., a man aged 32, was admitted as an emergency with mental confusion, anuria and pain and tenderness on deep palpation of right loin. The blood urea nitrogen was 133 mg. per cent. Cystoscopy and retrograde pyelogram revealed a solitary right kidney with rupture of a hydronephrotic pelvis (fig. 1, *A*). A simple nephrostomy relieved the hydronephrosis and resulted in rapid diuresis and cure. A check-up pyelogram showed a fairly normal kidney (fig. 1, *B*).

Case 2. R. A., a woman aged 38, was admitted to the general surgical service for removal of a large ovarian cyst. She was totally anuric for 4 days postoperatively, when cystoscopy and retrograde pyelogram showed severance of the left ureter with the upper segment tied and ligature of the right ureter (fig. 2, *A*). The blood urea nitrogen was 88 mg. per cent, blood pressure 158/88. Marked abdominal distention and moderate edema were present. The upper end of the

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Read at annual meeting, North Central Section of American Urological Association, Detroit, Mich. October 7–9, 1954.

[1] Meroney, W. H. and Herdon, R. F.: The management of acute renal insufficiency. J. A. M. A., 155: 877, 1954.

* Acute uremia secondary to obstructive uropathies: 1) congenital strictures of meatus; 2) congenital contraction bladder neck; 3) bladder neck obstructions, acquired; 4) bilateral ureteral obstructions due to stones or tumors; 5) bilateral hydronephrosis due to aberrant vessels or bands; 6) obstruction of collecting tubules due to sulfa or uric acid crystals.

FIG 1 C C, man aged 32 Acute clinical uremia from ruptured solitary hydronephrotic kidney *A*, simple nephrostomy drainage, cure. *B*, excretory urogram 6 months after uremia.

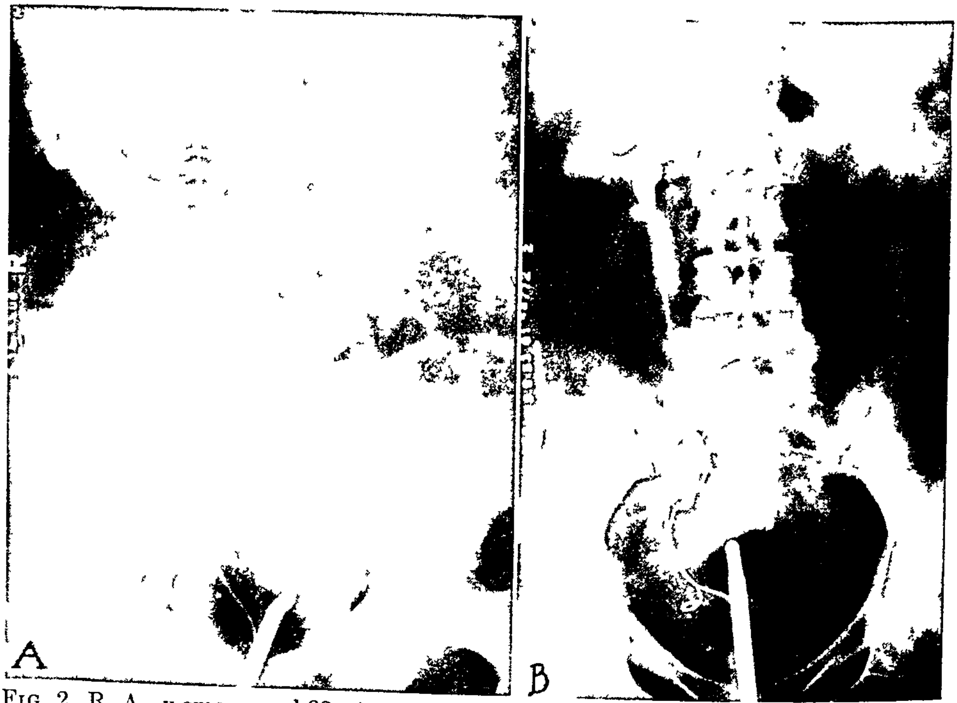

FIG 2 R A, woman aged 38 *A*, fourth day of anuria with ligature about right ureter and ligature with severance below left ureter *B*, pyelograms show residual stricture of right ureter

left ureter was implanted into the dome of the bladder, and the ligature of the right ureter was removed with a splinting catheter left indwelling A residual stricture of the right ureter with some hydronephrosis resulted (fig 2, *B*)

Acute uremia may occur from either acute or chronic obstructive conditions that produce an acute anuria

ACUTE UREMIA SECONDARY TO FLUID AND ELECTROLYTE IMBALANCES

The group of lesions* that cause renal insufficiency from fluid and electrolyte imbalances is a large and important one Although the disease is primarily of some other organ, the resultant fluid or electrolyte imbalance reflects itself through the kidney, resulting in renal insufficiency Clinical uremia may not occur since treatment of the underlying cause will effect a rapid cure If the renal insufficiency persists for several days, then degenerative changes occur in the kidney parenchyma and force the patient into the third group of intrinsic lesions of the kidney Such a condition is many times fatal

ACUTE UREMIA SECONDARY TO INTRINSIC RENAL LESIONS

The third group of etiologic agents that produce acute renal insufficiency are those directly affecting the kidney parenchyma They are the most serious and difficult to treat Once the kidney damage has occurred, no amount of surgery or forcing of fluids will be of any value, but on the contrary may induce a rapid onset of clinical uremia and death Much progress has been made during the past decade in prevention and treatment of this group, perhaps stimulated by Kolff's[3] classic development of the artificial kidney During this period the mortality rate in acute uremia is said to have been reversed from 90 per cent death rate reported by Lucké[4] to a survival rate averaging 75 per cent (Bull et al [5] and Muirhead et al) [6] It has been our experience that the mortality rate of acute uremia is still over 50 per cent Much of this is based upon seeing a large number of cases of terminal acute uremia patients sent to us for dialysis

Many names have been used to describe the intrinsic group of lesions such as lower nephron nephrosis and mercury nephrosis Regardless of the agent, they all have the common characteristic of acute renal failure Although the pathological process may differ slightly, the one common denominator is the ability of the kidneys to regenerate and function again, that is, provided the patient

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* Acute uremia secondary to fluid and electrolyte imbalance 1) vomiting, protracted, i e , intestinal obstruction, 2) diarrhea, i e , cholera, dysentery, etc , 3) fistula from small intestine, 4) intestinal hemorrhage, 5) abortion, septic, 6) cardiac failure, 7) dehydration following surgery, 8) heat stroke, 9) diabetic acidosis, 10) addisonian crisis, 11) atomic and x ray irradiation, 12) allergic reactions, 13) anoxia, i e , cardiac standstill, 14) infections of severe toxicity, 15) intravascular hemolysis, 16) pulmonary infarct, 17) poison oak, 18) mushroom poisoning, 19) bacitracin

[2] Wakim, K G Physiological basis for anuria Proc Staff Meet , Mayo Clinic, **29**: 65, 1954

[3] Kolff, W J and Berk, H T J Artificial kidney, dialyzer with great area Geneesk gids, **5**: 21, 1943

[4] Lucké, B , Lower nephron nephrosis Mil Surg , **99** 371-396, 1946

[5] Bull, G M , Joekes, A M and Lowe, K G Conservative treatment of anuric uremia Lancet, **2**: 229, 1949

[6] Muirhead, E E , Vanatta, J and Grollman, A Acute renal insufficiency Arch Int Med , **83**: 528, 1949

TABLE 1. *Acute uremia secondary to intrinsic renal lesions*

A. Circulatory.	B. Nephrotoxic.	C. Glomerular-Tubular.
1. Traumatic shock	1. Bichloride mercury	1. Acute glomerular nephritis
2. Surgical shock	2. Bismuth	2. Bilateral cortical necrosis
3. Obstetrical shock	3. Potass. dichromate	3. Fat emboli
4. Transfusion reaction	4. Potass. chlorate	4. Eclampsia
5. Crush syndrome	5. Ethylene glycol	5. Toxemia of pregnancy
6. Burns, severe	6. Sulfonamides	6. Amniotic fluid emboli
7. Hepato-renal syndrome	7. Barbitals	
8. Aortograms	8. Aspirin	

lives long enough for this to take place. Apparently regeneration starts almost immediately after the renal damage has occurred.

The intrinsic group of agents producing acute uremia may well be classified into three sub-groups: 1) circulatory; 2) nephrotoxic; 3) glomerulotubular.

PREVENTION OF ACUTE UREMIA FROM INTRINSIC CIRCULATORY ORIGIN

The prevention of acute uremia arising from the intrinsic circulatory origin has a wide field of application (table 1). Surgical, traumatic or obstetrical shock associated with hemorrhage is one of the most common causes of acute uremia. A state of shock of several hours' duration frequently results in anuria. Vigorous efforts should be made to bring the patient out of shock by rapid restoration of the depleted blood volume with whole blood. Where no blood is available, then plasma expanders should be used. Pooled plasma is not only expensive but carries the additional hazard of acute hepatitis.

Acute uremia following mismatched transfusions is difficult to explain but it occurs in spite of all efforts to prevent them. If careful watch is kept on the patient by the nurse when a reaction occurs, immediate discontinuance of the transfusions will often prevent anuria. It has been shown that when less than 300 cc of mismatched blood has been given,[7] serious results did not occur, whereas the full 500 cc carried a mortality of 50 per cent. Immediate alkalinization with intravenous soda bicarbonate[8] is said to help prevent the formation of acid hematin casts. Using the theory that alkalinization will prevent acid hematin, all the patients on our service receive 11.75 gm. of soda bicarbonate in water to be given intravenously just before the transfusion. Over a period of 14 years no patients on our service had hemolysis although we do not know of any mismatched transfusions being used. However, during the same period at least one or more mismatched transfusions were given to other patients each year. Antihistamines will not prevent the hemolytic reactions. Acute hemolysis following transurethral surgery can be prevented by using glycine as the irrigant.

PREVENTION OF ACUTE UREMIA OF INTRINSIC NEPHROTOXIC ORIGIN

Nephrotoxic agents are a common source of acute uremia (table 1). They are many times overlooked as the causative agent. It is well known fact that alkalinization will prevent precipitation of acetyl crystals of the sulfa drugs but it will not prevent the nephrotoxic reaction. Since the sulfa drugs are so commonly used, they must always be under suspicion as the cause of anuria. Carbon tetrachloride is another drug that is commonly overlooked as the source of acute uremia. Inhalation of the fumes in a closed space plus the consumption of alcohol may produce both acute liver and kidney damage. Bichloride of mercury, arsenic and gold poisoning require the immediate use of BAL, 5 mg./kg. followed by 2.5 mg./gm. every 2 hours for the first 24 hours. This, in combination with other treatment, will often prevent acute kidney damage. Phenobarbitals, aspirin, and bromides can be dialyzed out of the patient, before kidney damage occurs, by means of the artificial kidney.

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[7] Daniels, W. B., Leonard, B. W. and Holtzman, Saul: Renal insufficiency following blood transfusions. J. A. M. A., **116:** 1208, 1941.

[8] Varney, J. H., Cohen, J. K. and Cawley, J. J.: Successful treatment of mismatched blood transfusion. J. A. M. A., **145:** 978, 1951.

TREATMENT OF THE PRE-UREMIC PHASE

Three fundamental principles are used in the treatment of the pre-uremic phase: 1) Restrict fluids to prevent pulmonary and cerebral edema. 2) Reduce nitrogen catabolism. 3) Electrolyte balance should be kept as near normal as the situation requires. These principles are based on the regeneration and function of the kidneys with acute renal failure. Renal function may return any time from the third to the thirty-first day after onset of anuria. The problem is then to keep the patient alive until a return of normal kidney function.

FLUIDS IN THE PRE-UREMIC PHASE

Fluids should be restricted to 800 cc daily plus the previous 24 hour output of urine, vomitus, estimated diarrhea loss, fistula drainage, and gastro-intestinal suction. If the patient is already edematous, then only the previous day's output is replaced. Dehydrated patients should not be overloaded with fluids. Fever requires some additional fluids. Most patients can take fluids by mouth at the onset, but eventually require parenteral administration. Glucose 10 per cent in water is the best solution. Salt solutions as a rule are contraindicated.

Weigh the patient daily. Any gain in weight is probably due to fluids. An accurate intake and output record is kept. An indwelling catheter is always inserted with direct drainage to a sterile bottle. At least twice a day the catheter is irrigated with a measured amount of fluid to determine the patency.

PROTEIN CATABOLISM IN THE PRE-UREMIC PHASE

The diet is carefully controlled to reduce protein catabolism. This is a high fat, high carbohydrate, low protein, salt and potassium diet. Lip-O-Mul (Upjohn) has been found to be the most satisfactory food supplement as a 50 per cent solution, either 40 cc per hour by mouth or 1000 cc per day by stomach tube. This will provide adequate calories. If food is not tolerated then glucose 10 per cent in water intravenously 1000 to 1200 cc per day will give from 400 to 500 calories. A caloric intake will help prevent acidosis of starvation. Cortisone is contraindicated. Testosterone 50 mg. daily helps nitrogen balance.

Fever, infected tissue, pools of blood and proteins in the diet will markedly increase the nitrogen retention. Adequate doses of antibiotics should be used to control infection and prevent pneumonia. Adequate drainage of abscesses and vigorous debridement of wounds are important. Frequent change of position essential.

ELECTROLYTE BALANCE IN THE PRE-UREMIC PHASE

Acidosis progresses very rapidly due to the accumulation of acids. When the CO_2 combining power falls below 20 volumes per cent, some type of corrective therapy is indicated. No attempt is made to restore the CO_2 to normal since the acidosis is due to accumulation of acids rather than to a loss of base. Sodium bicarbonate in 3 per cent to 5 per cent solutions freshly prepared will effect a rapid improvement. The use of 1/6 molar lactate will give a more gradual rise.

Hypochloremia is quite common as a result of vomiting. Here again no attempt is made to restore the sodium of chlorides to normal because pulmonary and cerebral edema or cardiac failure may result. Where the sodium is low and the potassium high, careful replacement will help combat the potassium.

Hyperpotassemia is by far the most important and dangerous electrolyte causing the majority of deaths from cardiac standstill. Potassium is derived from tissue damage, blood destruction, diet and blood transfusion. A daily blood potassium and electrocardiographic study should be made to follow the progress of potassium. There are several methods of combating excess potassium such as continuous intravenous glucose with or without insulin, one unit per 3 gm. of glucose; continuous slow intravenous calcium gluconate; intravenous normal saline but not continuous; and digitalis. Ion exchange resins may be tried but are usually not effective in these sick patients. As a rule, the blood pressure rises during the pre-uremic phase but with potassium intoxication the blood pressure falls and the heart sounds become weak along with generalized muscular weakness.

The red blood count is markedly reduced in acute uremia. This is a difficult problem to solve because all transfusion blood has considerable potassium and the older the blood the more it contains. With an already elevated blood potassium, the giving of several transfusions may prove fatal. We have observed this to happen on several patients. It is best to disregard the blood count unless it is below 2 million, then only small transfusions of freshly drawn blood or washed packed red cells should be given. No attempt should be made to return the blood count to normal.

Calcium is usually depressed while phosphorus is elevated paralleling the potassium. Calcium is a direct antagonist to potassium but must be given as a continuous drip to be of any value. Meroney and Herdon[1] believe that digitalis has an additive effect with calcium in combating potassium. They feel that giving calcium and digitalis together when a dialysis is applied may prove dangerous by removing the potassium leaving the patient with digitalis intoxication.

TREATMENT OF THE ACUTE UREMIC PHASE

The acute uremic phase occurs anywhere from the third to the twelfth day after onset of the acute renal failure. This phase can be recognized by the presence of marked abdominal distention, continuous vomiting and hiccups, hyperactive

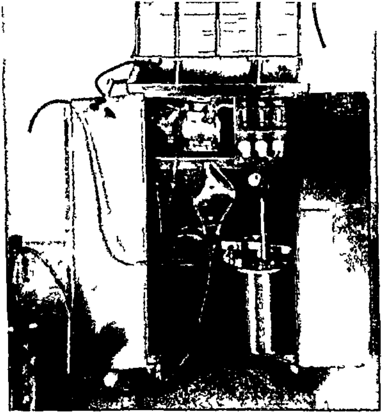

FIG 3 Allen Keitzer modification of Skeggs Leonards artificial kidney ready for application to patient Sixteen units in dialyzer

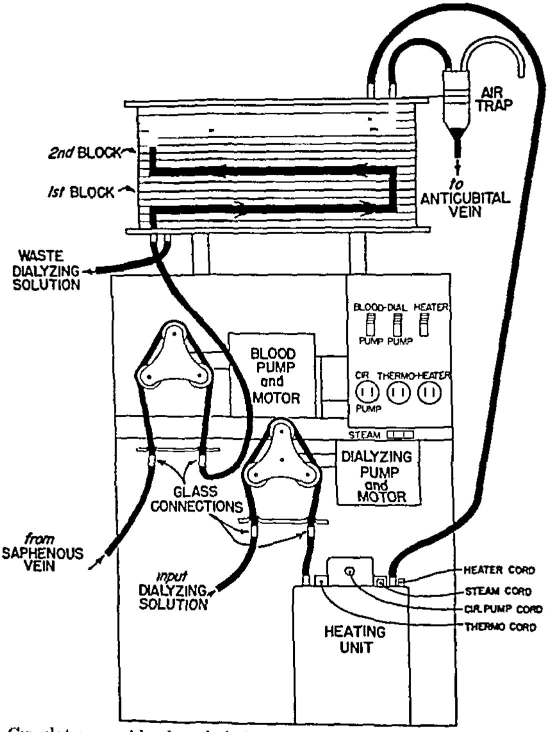

FIG. 4 Circulation in blood and dialyzing circuits in Allen-Keitzer modification of Skeggs Leonards artificial kidney

muscles with intermittent twitching and jerking of the extremities, occasional carpo-pedal spasm, mental confusion, coma and various degrees of cyanosis. The blood pressure is usually elevated to hypertensive levels unless the toxicity of potassium produces hypotension with muscular weakness. Pericarditis is a serious sign. Edema may be present with cerebral or pulmonary edema at times.

When clinical uremia appears and diuresis has not begun, then we are treating a patient whose chances of survival are less than 50 per cent.

The time to do artificial dialysis is not after clinical uremia has occurred but rather just before it appears. The application of the artificial kidney is not too difficult and apparently is a fairly harmless procedure. Potential bleeding has been no contraindication. With artificial dialysis by means of the mechanical kidney, the waste nitrogens can be reduced to safe levels, the electrolytes placed in balance and if the patient is edematous the fluid can be ultrafiltrated out at the rate of over 1000 cc per hour.

We use our own modification of the Skeggs-Leonards artificial kidney with 16 units instead of the 12 units (figs. 3, 4, 5). This will reduce the blood urea nitrogen 40 mg. per cent per hour so that 4 hours' dialysis will accomplish all that is necessary.

Case 3. E. B., aged 49, had a dilatation and curettage for hemorrhage because

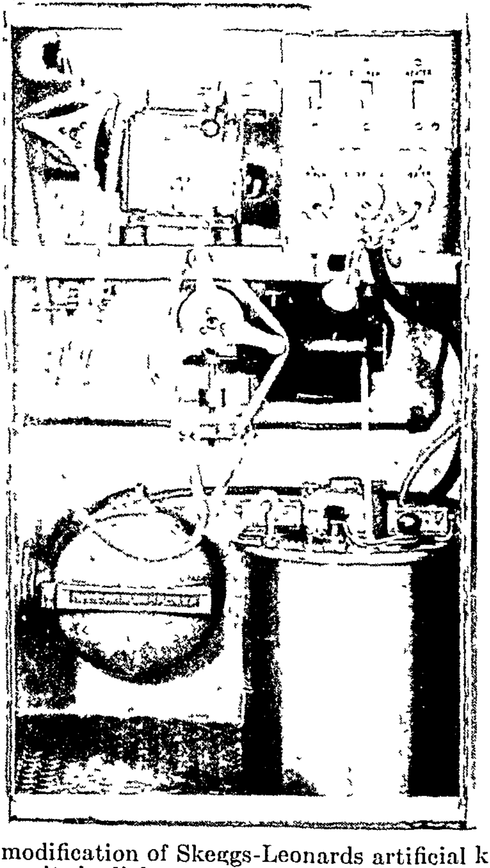

FIG. 5. Allen-Keitzer modification of Skeggs-Leonards artificial kidney ready for application to patient. Sixteen units in dialyzer.

the red blood cell count was 2.6 million, on September 5, 1954. She was given two units of mismatched blood, and anuria developed immediately. On the fifth day of anuria, she was transferred to our service for treatment. On the tenth day of anuria she was mentally confused, had muscle twitching, some gain in weight, blood urea nitrogen of 176 mg. per cent. She was dialyzed on the morning of the eleventh day reducing the blood urea nitrogen to 30 mg. per cent. On the thirteenth day dialysis commenced and the patient recovered.

DIURETIC PHASE

The onset of diuresis does not mean that the patient is over the critical period since it takes several days before the kidneys will excrete anything except highly dilute urine. The nitrogen wastes continue to accumulate while varying amounts of electrolytes are lost. The 24 hour output of salt and potassium is measured and replaced the following day.

SUMMARY

Acute uremia is caused by many different etiologic agents which may be classified into obstructive uropathies, the fluid and electrolyte imbalances, and the intrinsic renal lesions. Prevention is worthwhile since the mortality in acute uremia is still over 50 per cent.

The treatment of acute uremia is divided into the pre-uremic phase where three principles are followed: 1) restrict fluids, 2) reduce catabolism, 3) correct electrolytes within reason. The treatment of the uremic phase requires artificial dialysis. The diuretic phase requires careful watch of the electrolytes lost in the urine.

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STUDIES ON THE MECHANISM OF FORMATION OF RENAL CALCULI, I

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The physiological conditions which in one individual lead to the formation of renal calculi and in another do not, have long been a matter of urological interest. In considering this question, it has seemed likely that the stone-forming individual is producing urine which is supersaturated, or at least more supersaturated, with regard to such constituents as calcium, phosphate and oxalate than does the normal subject. If no such difference exists, the distinction might lie in the degree of protection afforded by urinary colloids or by some other circumstance which might prevent precipitation.

Equilibrium conditions in urine have been studied by Flocks. In a series of papers, he reported the results of determining the concentrations of calcium and of phosphate in samples of urine, both as passed and after shaking for a short time with some solid tricalcium phosphate. Most of the data submitted by Flocks concern the calcium content of the urine, before and after shaking a 50 ml. sample 10 minutes with 1 gm. finely divided calcium phosphate. He designates the resulting change in calcium content (presumably expressed in mg. Ca per 100 ml. urine) as positive when the equilibrated sample has increased in its calcium content, thus denoting a previously unsaturated solution, and as negative when a decrease is observed, thus denoting previous supersaturation. These values, positive or negative, are referred to as the calcium precipitability of the urine.

In order to ascertain whether such principles could be applied to the urinary system, we have extended and elaborated the observations of Flocks. We have thought it pertinent to extend the equilibration procedure to the use of other solid phases besides tricalcium phosphate. For example, in spite of the higher solubility of secondary calcium phosphate, the usual pH of most urine samples would make the latter appear to be a more likely solid phase than would the tribasic salt. We have therefore included equilibration experiments using both calcium phosphates. The presence of calcium oxalate in many calculi suggested its use in addition to the above. Furthermore, realizing that a supersaturated solution may often be seeded and precipitation started by any mechanical means, we have duplicated these experiments using only a small sample of glass wool or powdered glass as the solid phase.

In these experiments reported below, only tricalcium phosphate and calcium oxalate were used as solid phases and the determinations comprised pH, calcium, phosphate and oxalate. The following procedures were used for these determi-

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nations, all of which were made on the urine samples both before and after equilibration:

pH. The glass electrode was used.

Calcium was determined on the phosphate-free urine by titration with ethylenediaminetetra-acetate at pH 11 using ammonium purpurate as indicator.

Phosphate was determined by the colorimetric method of Gomori.

Oxalate was determined by the method of Simpson. This consists essentially in extraction of the acidified urine with ether, subsequent precipitation of the oxalate as calcium oxalate and titration of the latter, in sulfuric acid solution by means of standard permanganate.

EXPERIMENTAL

The concentrations of the normal urinary constituents are obviously subject to wide variations, depending on the daily volume. In considering questions of degree of saturation, it is the concentration of the various constituents that is of importance, rather than the 24-hour output. We have therefore expressed our analytical figures in terms of molar or millimolar concentrations.

Filtration of samples. Since many urine samples are cloudy and it is generally assumed that the solid phase in such cases is amorphous calcium phosphate we have determined the effect of various methods of filtration. Comparisons were made using suction filtration through Whatman No. 42 and No. 50 papers as well as through fine-grade sintered glass filters. Although the differences between the effects of these two grades of paper were small, a somewhat better removal of the suspended matter was obtained with Whatman No. 50 paper. Filtration through sintered glass gave equally good results but was much slower. The practice followed, therefore, in all subsequent work, was to filter the urine sample through the No. 50 paper before any equilibration studies, whether it appeared clear to the eye or not.

The question arises as to why, if the urine has been, before and after passing, in contact with a finely divided suspension of calcium phosphate, it should not already have attained equilibrium with that solid phase. Nevertheless, we have usually found that these filtered urines showed themselves to be supersaturated when shaken with solid crystalline phosphate or oxalate and in the interests of uniformity we have continued using this preliminary filtration. An example of the effect of such a procedure on a normal 24 hour sample is as follows:

Unfiltered urine: Calcium, 2.76×10^{-3} moles per l.; oxalate, 5.50×10^{-4} moles per l.; phosphate, 3.91×10^{-2} moles per l.

Filtered urine: Calcium, 2.42×10^{-3} moles per l.; oxalate, 4.90×10^{-4} moles per l.; phosphate, 3.88×10^{-2} moles per l.

Decreases due to filtration: Calcium, 3.4×10^{-4} moles; oxalate, 6.0×10^{-5} moles; phosphate, 3.0×10^{-4} moles.

The sum of the decreases of the two anions (phosphate and oxalate) is 3.6×10^{-4} moles per l. This figure compares favorably with that of 3.4×10^{-4} moles for the decrease in the calcium if one is to assume that the suspended material removed consisted of a small amount of calcium oxalate with some *secondary* calcium phosphate ($CaHPO_4$), i.e. a 1:1 molar ratio of calcium to phosphate. If, on the other hand, we assume the suspended material to be tricalcium phosphate ($Ca_3(PO_4)_2$), 3.0×10^{-4} moles of phosphate would require 4.5×10^{-4} moles of calcium. This, plus the equivalent of the oxalate, calls for a total of 5.1×10^{-4} moles of calcium. This amount is outside the experimental error of our calcium determinations and leaves us forced to assume that either some other undetermined cation, such as magnesium, must make up the difference or that we are here dealing with, not the tertiary, but the secondary calcium phosphate. Considering the fact that most normal urines have pH values averaging about 6, and taking into account the solubility products of these salts and the dissociation constants of phosphoric acid, it would seem much more likely that the amorphous suspension we are here removing, as well as formed calculi should consist of the secondary phosphate. Examination of the literature dealing with analyses of renal calculi reveals much qualitative but very little quantitative data. Only on the latter could one base any calculations as to the molar ratios of anions and cations. Indirect evidence, however, exists favoring the possible formation of the secondary phosphate (Melon and Dallemagne) although examination with the polarizing microscope has, in the hands of some workers, given support to such structures as apatite and substituted apatites in naturally formed calculi (Carr and Philipsborn) while the data reported by Jensen and by Prien and Frondell still lend support to the prevalence of apatite in calculi. Nevertheless much more quantitative evidence than at present exists would be highly desirable.

Comparisons are also of interest between the solubility products of calcium oxalate and the calcium phosphates in water and in urine. In pure water, the most commonly quoted values are as follows:

$$Ca^{++} \times C_2O_4 = 2.57 \times 10^{-9} \text{ (25°C.)}$$

$$Ca^{++} \times HPO_4 = 1.0 \times 10^{-6}$$

$$(Ca^{++})^3 \times (PO_4)^2 = 1.0 \times 10^{-26}$$

The values for the calcium phosphates are less definite due to obvious complications of hydrolysis etc.

Our solubility products, for calcium oxalate in urine, range, before equilibration, from 0.6 to 4.6×10^{-6} for both normal and stone-forming subjects. It should be noted that these values are about 1000 times larger than the value in pure water. Medes, in 1932, reported that the solubility of calcium oxalate increases with increasing concentrations of urea. Assuming the average concentration of urea in urine, Medes' figures indicate about 1.0 mg. calcium oxalate monohydrate per 100 ml. urine, giving a solubility product of 4.7×10^{-9}. This, however, is entirely inadequate to account for our figures. Even at 37°C the solubility of calcium oxalate reported by Snapper, Bendein and Polok in 2 per cent urea solution corresponds to a solubility product of 4.8×10^{-8}, still about 1 per cent of the values we find in urine. Even after attainment of equilibrium with solid calcium oxalate, the product of the two still averages 8.8×10^{-7}, a

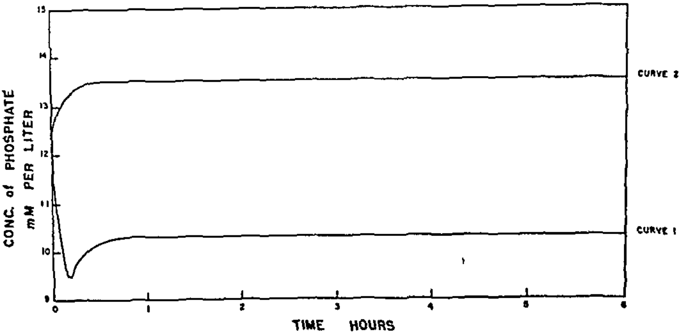

Fig. 1. Speed of equilibration of urine with calcium phosphates. pH of urine sample: 6.5
Curve 1. Equilibration with 1 gm. tricalcium phosphate per 100 ml. urine.
Curve 2. Equilibration with 1 gm. dibasic calcium phosphate per 100 ml. urine.

value about 35 times that of pure water at the same temperature. It is obvious that other factors besides the urea content must be operating.

One feature of these studies merits special attention. The conditions employed by Flocks in his studies consisted in shaking, presumably by hand, 1 gm. of tricalcium phosphate with 50 ml. of the urine for 10 minutes. We felt it to be extremely unlikely that a true equilibrium could be attained in that brief period and have therefore made a series of longer runs in which samples of the urine were withdrawn at varying times and the phosphate content determined. By confining our determinations to this one, quickly determined constituent, much time was saved.

Some of the results are shown in figures 1 and 2. These curves were obtained by shaking 100 ml. samples of urine in a mechanical shaker for periods up to 18 hours. At intervals of 10, 20 and 30 minutes and of one hour on, samples were withdrawn, filtered and their phosphate content determined by the Gomori method. It was soon apparent that equilibrium was attained after about 4 hours shaking. The results of longer periods of shaking are therefore not included in these curves. However their form during the first half-hour is highly interesting in view of the results reported by Flocks. When tricalcium phosphate was used as the solid phase, a more or less sharp drop in phosphate content with a minimum reached in 10 to 20 minutes was nearly always obtained. After passing this minimum, the phosphate content rose to a plateau which was usually lower than the value in the original urine. Figures 1 and 2 show two examples of this effect in urines from two different normal subjects. Curve 1 of figure 1 is an especially outstanding example of this effect. The corresponding curve in figure 2 shows a less spectacular drop and is representative of the majority of urine samples we have examined. It is evident, however, that a 10-minute period of shaking with tricalcium phosphate does not, in our experience, produce equilibrium results as regards phosphate. We find no correlation between the magnitude of this drop and the pH of the sample.

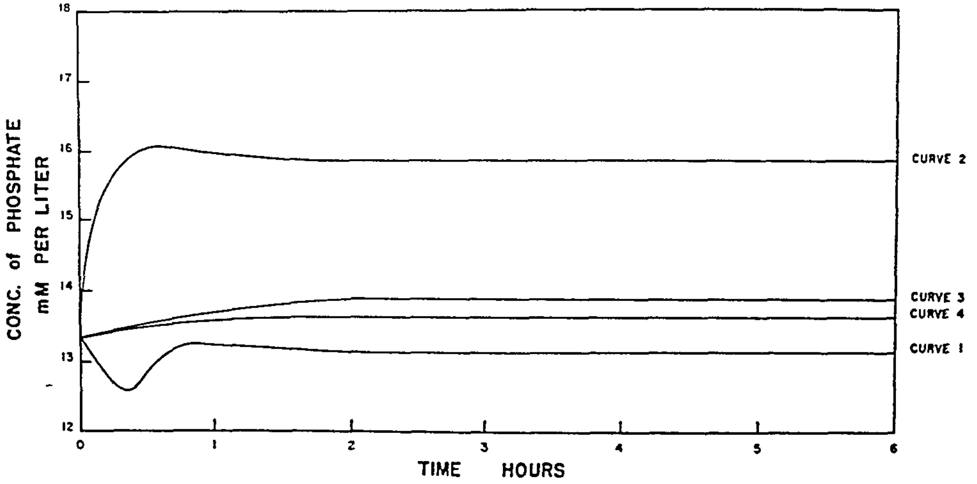

Fig. 2. Speed of equilibration of urine with different solid phases. pH of urine sample: 5.5

Curve 1. Equilibration with 1 gm. tricalcium phosphate per 100 ml. urine.
Curve 2. Equilibration with 1 gm. dibasic calcium phosphate per 100 ml. urine.
Curve 3. Equilibration with 1 gm. calcium oxalate per 100 ml. urine.
Curve 4. Equilibration with 1 gm. powdered glass per 100 ml. urine.

It will be noted from curves 3 and 4 of figure 2 that shaking with either solid calcium oxalate or an inert solid phase such as powdered glass, has very little effect on the phosphate content of the urine.

EQUILIBRATION DATA

The following experiments show, in terms of molar ratios, the reduction in the content of calcium, phosphate and oxalate of several samples of urine on equilibration in order to obtain some clue as to the composition of the salt which precipitates out when the urine is in contact with a solid phase. These samples were obtained both from normal individuals and from some habitual "stone formers". The 24-hour samples were analyzed for these three constituents both before and after about 12 hours mechanical shaking at room temperature with a uniform sample of the solid phase, in the proportion of 1 gm. of the solid to 100 ml. urine. In table 1 there are tabulated the results obtained by equilibration with tricalcium phosphate of twelve different samples from five different subjects (two normal and three forming calculi). Table 2 records the results of the same treatment of the same urine samples with calcium oxalate. In both tables column 1 records the identity of the sample and column 2 the subject and his history. Columns 3, 4 and 5 record the calcium content expressed as moles per liter multiplied by 10^3, before equilibration, after equilibration and the resulting loss. Columns 6, 7 and 8 record the same data for the phosphate content using a factor of 10^2. Columns 9, 10 and 11 record the same data as regards oxalate content using a factor of 10^4. In column 12 is recorded the discrepancy between the sum of the loss, in molar terms, of anions (phosphate plus oxalate) and of the calcium. It will be observed that with the two normal subjects the loss by precipitation was usually definitely greater in the case of the two anions than in the case of the calcium showing that some other metal besides calcium was involved. These

TABLE 1 *Molar ratios between loss of calcium, phosphate and oxalate on equilibration of urine samples with tricalcium phosphate*

1	2	3	4	5	6	7	8	9	10	11	12	13	14
Sample	Subject & History	Calcium (moles per l $\times 10^3$)			Phosphate (moles per l $\times 10^3$)			Oxalate (moles per l $\times 10^5$)			Decrease $\times 10^3$	Solubility Products	
		Before equil	After equil	Decrease	Before equil	After equil	Decrease	Before equil	After equil	Decrease	Anions minus calcium	$Ca^{++} \times {}^{=}HPO_4$ Before After	$Ca^{++} \times {}^{=}C_2O_4$ Before After
1	R. G. Normal	3.60	3.30	0.30	5.45	4.74	0.71	5.15	4.91	0.24	6.82	1.96×10^{-4} 1.56×10^{-4}	1.85×10^{-6} 1.62×10^{-6}
2	R. G. Normal	5.00	3.75	1.25	4.78	4.38	0.40	3.15	2.82	0.33	2.78	2.39×10^{-4} 1.64×10^{-4}	1.57×10^{-6} 1.06×10^{-6}
3	R. G. Normal	4.28	3.82	0.46	6.00	5.69	0.31	5.05	4.80	0.25	2.66	2.57×10^{-4} 2.17×10^{-4}	2.16×10^{-6} 1.84×10^{-6}
4	I. S. Normal	2.75	1.55	1.20	1.94	1.82	0.12	2.42	2.45	0	0	5.34×10^{-5} 2.82×10^{-5}	6.65×10^{-7} 3.80×10^{-7}
5	I. S. Normal	2.68	2.50	0.18	2.24	2.20	0.04	3.46	3.34	0.12	0.23	6.00×10^{-5} 5.50×10^{-5}	9.28×10^{-7} 8.34×10^{-7}
6	I. S. Normal	2.47	1.53	0.94	2.06	1.89	0.17	3.71	3.32	0.39	0.80	5.08×10^{-5} 2.86×10^{-5}	9.16×10^{-7} 5.08×10^{-7}
7	H. C. Stones	4.11	3.17	0.94	2.98	2.97	0.01	6.97	5.97	1.00	−0.74	1.22×10^{-4} 0.94×10^{-4}	2.87×10^{-6} 1.89×10^{-6}
8	H. C. Stones	3.02	2.85	0.17	2.30	2.28	0.02	5.57	4.82	0.75	0.10	6.94×10^{-5} 6.50×10^{-5}	1.68×10^{-6} 1.37×10^{-6}
9	H. C. Stones	6.70	5.76	0.94	3.25	3.22	0.03	6.92	4.62	2.30	−0.41	2.18×10^{-4} 1.85×10^{-4}	4.64×10^{-6} 2.66×10^{-6}
10	B. L. Stones	1.43	1.16	0.27	0.46	0.45	0.01	4.60	3.33	1.27	−0.04	6.58×10^{-6} 5.22×10^{-6}	6.58×10^{-7} 3.86×10^{-7}
11	B. L. Stones	1.77	1.39	0.38	0.29	0.27	0.02	3.41	3.29	0.12	−0.17	5.13×10^{-6} 3.75×10^{-6}	6.04×10^{-7} 4.57×10^{-7}
12	C. H. Stones	3.03	2.25	0.78	1.90	1.73	0.17	2.78	2.39	0.39	0.96	5.76×10^{-5} 3.89×10^{-5}	8.42×10^{-7} 5.38×10^{-7}

calculations are based on the most simple assumption, namely, that any salt lost by precipitation contains a 1:1 ratio of calcium to the divalent anion. This assumes therefore, precipitation of *secondary* calcium phosphate. If we assume, instead, precipitation of the tertiary salt, each mole of phosphate would require 1.5 moles calcium and the discrepancies in column 12 would be still greater. It seems obvious that normal subjects as a rule precipitate, on equilibration a mixture of salts of calcium and of some other metal, most likely magnesium.

As would be expected, the relative decrease in oxalate is greater on equilibration with calcium oxalate while the relative decrease in phosphate is greater when tricalcium phosphate is used. However, since the molar concentration of oxalate is roughly about one per cent of that of the phosphate, variations in oxalate content and oxalate loss have less effect on the balance between anions and cations. The chief effect, especially with stone-formers, appears to be the result of a lower degree of loss of phosphate on equilibration. As a result, two of our three stone forming subjects show a small excess of calcium loss over loss

TABLE 2. *Molar ratios between loss of calcium, phosphate and oxalate on equilibrium of urine samples with calcium oxalate*

1	2	3	4	5	6	7	8	9	10	11	12	13	14
	Subject & History	Calcium (moles per l. × 10^3)			Phosphate (moles per l. × 10^2)			Oxalate (moles per l. × 10^4)			Decrease × 10^3	Solubility Products	
Sample		Before equil.	After equil.	Decrease	Before equil.	After equil.	Decrease	Before equil.	After equil.	Decrease	Anions minus calcium	$Ca^{++} \times {}^{=}HPO_4$ Before After	$Ca^{++} \times {}^{=}C_2O_4$ Before After
1	R. G. Normal	3.60	3.23	0.37	5.45	4.77	0.68	5.15	3.15	2.00	6.63	1.96×10^{-4} 1.54×10^{-4}	1.85×10^{-6} 1.02×10^{-6}
2	R. G. Normal	5.00	4.65	0.35	4.78	4.35	0.43	3.15	1.86	1.29	4.08	2.39×10^{-4} 2.02×10^{-4}	1.57×10^{-6} 8.65×10^{-7}
3	R. G. Normal	4.28	3.76	0.52	6.00	5.55	0.45	5.05	2.68	2.37	4.22	2.57×10^{-4} 2.09×10^{-4}	2.16×10^{-6} 1.01×10^{-6}
4	I. S. Normal	2.75	1.70	1.05	1.94	1.80	0.14	2.42	1.14	1.28	0.48	5.34×10^{-5} 3.06×10^{-5}	6.65×10^{-7} 1.94×10^{-7}
5	I. S. Normal	2.68	2.50	0.18	2.24	2.20	0.04	3.46	1.55	1.91	0.41	6.00×10^{-5} 5.50×10^{-5}	9.28×10^{-7} 3.87×10^{-7}
6	I. S. Normal	2.47	1.87	0.60	2.06	1.90	0.16	3.71	2.38	1.33	1.13	5.08×10^{-5} 3.55×10^{-5}	9.16×10^{-7} 4.45×10^{-7}
7	H. C. Stones	4.11	4.08	0.03	2.98	2.95	0.03	6.97	3.63	3.34	0.60	1.22×10^{-4} 1.20×10^{-4}	2.87×10^{-6} 1.47×10^{-6}
8	H. C. Stones	3.02	2.82	0.20	2.30	2.28	0.02	5.57	3.37	2.20	0.22	6.94×10^{-5} 6.43×10^{-5}	1.68×10^{-6} 9.50×10^{-7}
9	H. C. Stones	6.70	6.05	0.65	3.25	3.25	0	6.92	3.52	3.40	−0.31	2.18×10^{-4} 1.97×10^{-4}	4.64×10^{-6} 2.13×10^{-6}
10	B. L. Stones	1.43	1.06	0.37	0.46	0.45	0.01	4.60	2.19	1.41	−0.13	6.58×10^{-6} 4.77×10^{-6}	6.58×10^{-7} 2.32×10^{-7}
11	B. L. Stones	1.77	1.22	0.55	0.29	0.27	0.02	3.41	1.21	2.20	−0.13	5.13×10^{-6} 3.29×10^{-6}	6.04×10^{-7} 1.48×10^{-7}
12	E. H. Stones	3.03	2.46	0.57	1.90	1.88	0.02	2.78	1.11	1.67	−0.20	5.76×10^{-5} 4.62×10^{-5}	8.42×10^{-7} 2.73×10^{-7}

of the two anions. Whether this behavior constitutes a real differentiation between the two classes of urines is a question requiring much more extensive data.

The solubility products in columns 13 and 14 are of interest in that, while they show definite decreases on equilibration, the final values are still far above those obtained in water solutions. The effect of all equilibrations on the pH of the urine sample was neither consistent nor of significant size.

Future plans contemplate more elaborate analyses. Because of the possibility that a part of the calcium in the sample is not actively ionic, we propose to include a general determination of complexing agents and a specific one for citrates. The role of citrate in forming calcium complexes and its relationship to calculus formation was suggested over ten years ago but appears to have received little attention (Kissin and Locks, Shorr and co-workers).

SUMMARY

Urines from both normal subjects and from subjects with a history of calculus formation have been equilibrated with both tricalcium phosphate and calcium oxalate The resulting changes in their content of calcium, phosphate and oxalate have been determined

This treatment, in practically all cases has resulted in a decrease in the concentration of the above constituents The molar ratios of these decreases have been used in an attempt to identify the salt or salts which precipitate out on such treatment To balance these molar ratios, the simultaneous precipitation of some other cation, such as magnesium, must be postulated

Investigation of the time required to attain equilibrium between the urine and the solid phase indicates a minimum of 1 hours Shorter periods of shaking (10 to 20 minutes) produce exaggerated and temporary decreases in the phosphate content, which later rises to a plateau level

Solubility product calculations for both secondary calcium phosphate and calcium oxalate show values for the former corresponding roughly to the values reported in pure water but for the latter values which are 100 or more times larger than the water values The normal urinary content of urea is far from sufficient to account for this increase

Some differences have been noted in the molar ratios of the loss of calcium, phosphate and oxalate on equilibration, between normal urines and those of calculus forming subjects

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TABLE 2. *Molar ratios between loss of calcium, phosphate and oxalate on equilibrium of urine samples with calcium oxalate*

1	2	3	4	5	6	7	8	9	10	11	12	13	14
		Calcium (moles per l. × 10^3)			Phosphate (moles per l. × 10^2)			Oxalate (moles per l. × 10^4)			Decrease × 10^3	Solubility Products	
Sample	Subject & History	Before equil.	After equil.	Decrease	Before equil.	After equil.	Decrease	Before equil.	After equil.	Decrease	Anions minus calcium	$Ca^{++} \times {}^{=}HPO_4$ Before After	$Ca^{++} \times {}^{=}C_2O_4$ Before After
1	R. G. Normal	3.60	3.23	0.37	5.45	4.77	0.68	5.15	3.15	2.00	6.63	1.96×10^{-4} 1.54×10^{-4}	1.85×10^{-6} 1.02×10^{-6}
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6	I. S. Normal	2.47	1.87	0.60	2.06	1.90	0.16	3.71	2.38	1.33	1.13	5.08×10^{-5} 3.55×10^{-5}	9.16×10^{-7} 4.45×10^{-7}
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8	H. C. Stones	3.02	2.82	0.20	2.30	2.28	0.02	5.57	3.37	2.20	0.22	6.94×10^{-5} 6.43×10^{-5}	1.68×10^{-6} 9.50×10^{-7}
9	H. C. Stones	6.70	6.05	0.65	3.25	3.25	0	6.92	3.52	3.40	−0.31	2.18×10^{-4} 1.97×10^{-4}	4.64×10^{-6} 2.13×10^{-6}
10	B. L. Stones	1.43	1.06	0.37	0.46	0.45	0.01	4.60	2.19	1.41	−0.13	6.58×10^{-6} 4.77×10^{-6}	6.58×10^{-7} 2.32×10^{-7}
11	B. L. Stones	1.77	1.22	0.55	0.29	0.27	0.02	3.41	1.21	2.20	−0.13	5.13×10^{-6} 3.29×10^{-6}	6.04×10^{-7} 1.48×10^{-7}
12	E. H. Stones	3.03	2.46	0.57	1.90	1.88	0.02	2.78	1.11	1.67	−0.20	5.76×10^{-5} 4.62×10^{-5}	8.42×10^{-7} 2.73×10^{-7}

of the two anions. Whether this behavior constitutes a real differentiation between the two classes of urines is a question requiring much more extensive data.

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Future plans contemplate more elaborate analyses. Because of the possibility that a part of the calcium in the sample is not actively ionic, we propose to include a general determination of complexing agents and a specific one for citrates. The role of citrate in forming calcium complexes and its relationship to calculus formation was suggested over ten years ago but appears to have received little attention (Kissin and Locks, Shorr and co-workers).

SUMMARY

Urines from both normal subjects and from subjects with a history of calculus formation have been equilibrated with both tricalcium phosphate and calcium

TABLE 1 *Patient P R*

Daily Specimen	Calcium Precipitability Prior to Hyaluronidase		Calcium Precipitability After Hyaluronidase	
	First Morning Specimen		First Morning Specimen	
1	−6 0	−8 8	−7 4	−8 8
2	−0 4	−8 8	−8 8	−11 0
3	−23 2	−13 2	−9 6	−10 8
4	−2 4	−12 0	−14 0	−16 0
5	−1 6	−10 0	−7 0	−10 0
6	+4 0	−8 0	−6 4	−7 2
7			−6 4	−6 6
8			−10 8	−7 6
9			−8 4	−12 0
10			−6 4	−13 2
11			−6 4	−9 2
12			−2 0	−6 8
13			−7 2	−4 0
14			−2 0	−0 4
15				−2 0

TABLE 2 *Patient W R*

Daily Specimen	Calcium Precipitability Prior to Hyaluronidase		Calcium Precipitability After Hyaluronidase	
	First Morning Specimen		First Morning Specimen	
1	−1 6	−3 2	−4 6	−5 0
2	−6 4	−7 2	−6 0	−8 4
3	−8 2	−7 2	−7 4	−5 2
4	−5 8	−9 2	−9 6	−10 8
5	−5 6	−3 2	−8 4	−5 6
6	−1 6	−2 4	−10 0	−6 0
7	−4 8	−4 2	−7 4	−8 0
8	−3 2	−7 6		−8 4
9	−5 2	−4 2		
10	−4 8	−7 2		

The study was begun by measuring the calcium precipitability of the patient's urine daily for several days prior to the administration of hyaluronidase Then, 300 turbidity units of hyaluronidase were administered twice daily for several days, and the calcium precipitability was again measured In 6 cases we selected the first morning specimen of the urine as well as the urine voided during the remainder of the day All but one of the individuals studied had urinary tract calculi at the time of the experiment During the studies the patients were maintained on a general hospital diet No attempt was made to measure the daily oral intake of calcium, since we felt that it remained fairly stable on the general diet In addition, we felt that unless the oral intake was extremely high, it would have little or no effect upon the urinary calcium output In all, 14 individuals were studied, and tables 1 and 2 are records of the values found

RESULTS

As noted from tables 1 and 2, the daily determinations of calcium precipitability both prior to and after administration of hyaluronidase varied as much as 13–15 units in these individuals. The remaining 12 patients had a similar response, and in no case was there less calcium precipitated from solution after the administration of hyaluronidase. In fact, so great a difference occurred in the values from day to day, both with and without hyaluronidase therapy, that the only conclusion which could be drawn was that hyaluronidase did not protect the calcium salts when measured by the calcium precipitability tests previously described.

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LEUKOPLAKIA OF THE RENAL PELVIS

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Leukoplakia of the renal pelvis is rare. McCrea at the Philadelphia General Hospital found not a single case in 46,928 autopsies and not one diagnosis of the condition in 251,578 admissions. Landes and Hamlin found less than 100 cases as of July 1954. Apart from the rarity of the lesion, the other reason for my report is to call attention to a diagnostic sign that is of great importance.

A 26-year old man presented himself in the office on May 1, 1950 complaining of pain in the left lower quadrant for 2 hours. The pain was so intense that he vomited while he was in the office. His pulse, temperature and respiration were normal. He presented the classical picture of renal colic. He had tenderness and rigidity over the left side of the abdomen. He had had similar attacks 1 month, 3 months and 1 year previously. Later questioning revealed that he had had attacks for the past 6 to 7 years. It was then elicited that once a year he had an attack of intense, drawing pain in the perineum and testicle for 4 to 5 hours and relief occurred at once when he passed a piece of tissue about 1 cm. by ⅓ cm. in size. Some of these attacks occurred while he was in the army but his case was not worked up.

The patient was admitted to St. Elizabeth Hospital that night for consultation because it was felt that the condition in the abdomen required surgery. He was seen by Dr. A. Vesper who stated in his notes that the patient presented an abdomen which was tender in the left lower quadrant, sudden muscular guarding 1 plus, no distention and no hernia. The kidney area was not tender and rectal examination was entirely normal. His impression was diverticulitis, left appendix, or renal lesion. Surgery was withheld.

At 2:00 a.m., up to which time the patient had received medication for his pain, he voided and stated that "it felt as though something broke loose." He immediately felt better. The urine was peculiarly gray and contained some gelatinous looking material, which the laboratory reported was an amorphous gelatinous mass with no cellular structure and as such could not be identified as peculiar to anything that had ever been seen.

On May 3 a flat film of the abdomen showed no abnormalities. Retrograde studies by Dr. W. Miner showed a normal right pyelogram. Retrograde studies of the left kidney showed good filling of the collecting system. There was, however, an irregular filling defect throughout the entire renal pelvis and the calyces to the lower pole. There was no evidence of hydronephrosis, definite caliectasis or of hydroureter. The changes described were rather difficult to evaluate, but it was felt that hyperplastic changes of the mucosa, leukoplakia, pyelitis cystica and neoplasm must all be considered. This was read by Dr. M. Walsh (fig. 1, *A*). As the material injected was drained a peculiar moth eaten appearance of the

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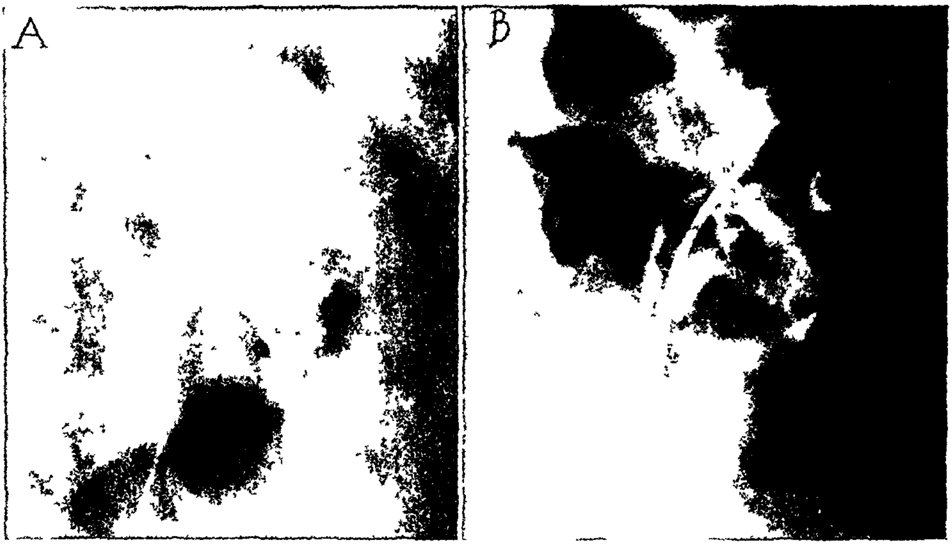

FIG. 1

pelvis was seen (fig. 1, *B*). A preoperative diagnosis of polyposis of the left kidney was made by Dr. W. Miner.

On May 5, operation was performed. The significant surgical notes stated: "The kidney was then mobilized and fat stripped from the pelvis of the kidney. After packing off the kidney pelvis, a longitudinal incision was made through it, to discern if our diagnosis of polyposis of the renal pelvis was correct or not. On incising the pelvis a grayish-black polypoid material extruded through the incision. A small amount of this was given to Dr. R. Ritterhoff, the pathologist, who pronounced it leukoplakia of the renal pelvis. It was deemed best to remove the kidney, after making the correct diagnosis. The kidney was removed." The patient made an uneventful recovery.

Pathological report: The gross specimen consisted of the left kidney and proximal 3 cm. of the ureter. It weighed 160 gm. and measured 12 by 6 by 4½ cm. The wall of the pelvis, which was moderately dilated, had been opened in the operating room and small portions of grumous, reddish-brown, friable substance submitted for frozen section. Those bits of friable tissue, on frozen section, revealed adult squamous epithelium. After removal of the organ the ureter and pelvis were opened. The distal 2½ cm. of the ureter was lined by a pink, focally hemorrhagic mucosa whereas that of the greater portion of the neck of the renal pelvis for a distance of 4½ cm. was lined by a wrinkled, shaggy, grayish-white membrane to which were adherent large, friable plaques of dirty brownish-yellow and gray substance from which the frozen section was taken. This grayish lining of the renal pelvis abruptly stopped at the division into the major calyces and these were lined by mucosa similar to that of the ureter. A calyx, probably a lower calyx, was distended by brownish, focally greenish, friable substance, and small masses of similar substance up to ½ cm. in diameter lay within the other divisions of the major calyces. The renal cortex measured approximately 7 mm. in thickness, was generally yellowish-tan, even and sharply de-limited from pinkish tan, symmetrical pyramids The renal surface was slightly lobulated and generally smooth and pale reddish-tan

Microscopic examination A section of the ureter and pelvis revealed a sharp transition in the type of mucosa Distally it was transitional There was then a focus of marked thinning and small strips of denuded mucosa and then a long strip of stratified squamous epithelium covered by a thick layer of cornified epithelial cells This mucosa rested upon a fibrosed, thickened and somewhat edematous and vascularized lamina propria Throughout the muscularis there were also fibrosis and inflammatory reaction, as is also true in the adventitia The inflammatory reaction within the submucosa was diffuse and macrophagic in type with moderate numbers of fibroblasts and lymphocytes The arteries within the adventitia presented moderate fibrosis of their intimal coats The stratified squamous lining was folded, moderately thick, of simple type and presented, in addition to the thick mat of cornified substance, a rather prominent stratum granulosum The mucosa of the calyces was of a transitional type Here again there was marked inflammatory reaction, edema and moderate fibroblastic proliferation in the supportive tissues Focally the mucosa of the calyces was denuded Sections of the kidney substance revealed moderate dilatation and also of the renal tubules and of Bowman's space The glomeruli, other than being compressed, appeared normal The epithelium of the tubules was somewhat granular and some of the tubules contained globular masses of acidophilic substance particularly in the proximal convoluted tubules Others contained fine inspissated protein in the loops of Henle and in the distal convoluted tubules to a lesser extent Many of the epithelial cells were distended by brownish orange, globular pigment This was felt to represent hemosiderin pigment or possibly bile, and an iron stain was ordered Finally, scattered throughout there were small scars in which there were numerous thin walled vessels and a sparse lymphocytic reaction Here again there was slight to moderate fibrosis of the intima of the small renal arteries Diagnoses (Dr J Ritterhoff) Extensive focal leukoplakia of the renal pelvis, marked chronic ureteritis and pyelitis, toxic nephrosis, moderate pigmentation of renal tubules possibly due to hemosiderin

The patient has remained well as of September 9, 1954

In a review of the history, it is significant that the patient stated that with each attack he passed something solid It took a year for each episode to occur and then after a passage of 6 or 7 years he had a 3-month interval and then a monthly interval in which this phenomenon occurred The examination of the material passed within 24 hours of his hospital admission did not help us Only the radiologist stated that leukoplakia had to be considered in the differential diagnosis Landes and Hamlin presented the third case known in which the correct diagnosis was made preoperatively In their case they were able to see and remove material projecting from the ureteral orifice which upon examination contained pathognomonic tissue Two years previously they made a tentative diagnosis on the basis of the patient's history because their patient had noticed "pieces of stuff that looked like skin" in his voided urine It is only with this experience of seeing an instance where a patient periodically passes tissue like material does our acumen now become evident and make us aware that the next time this happens, leukoplakia must be strongly considered.

SUMMARY

A case of leukoplakia of the kidney is presented. A history of the presence of soft, tissue-like substance passed from the urethra should make one suspect leukoplakia.

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URETEROPELVIC OBSTRUCTION IN INFANTS AND CHILDREN CLINICAL, RADIOLOGICAL AND EXPERIMENTAL STUDIES ON ELEVEN PATIENTS

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A review of the recent literature shows clearly the challenge offered to the surgeon by ureteropelvic obstruction, particularly in infants and children. In the past, numerous procedures have been proposed for the correction of this congenital malformation. Recently there have been reports of fairly good results in its treatment. Culp and DeWeerd[1] have proposed an operation in which a tongue of pelvic wall of the appropriate width and length is swung down beside the stricture in such a manner that a new ureteropelvic junction is formed. Their results in 12 patients are good. Miller[2] employed an elliptical end-to-end anastomosis, actually dividing the ureter and reimplanting it at an appropriate level. An inverting Connell suture of 5-0 chromic catgut was used in these anastomoses. Berneike and Deming[3] reported 30 cases of ureteropelvic obstruction. In these the stricture was excised and the anastomosis was performed over a T-tube. Interrupted everting sutures of 5-0 chromic catgut were employed. In 27 patients good anatomical and functional results were obtained.

The 11 cases presented in this series varied in age from 9 weeks to 12 years, nine were male, two were female. The symptomatology that brought these patients for medical attention was interesting. Four had no symptoms whatsoever, two had nausea and vomiting, two had recurrent fever, one failed to gain in weight, one had dysuria, one had a flank injury. On examination, four were found to have a mass, four were found to be underdeveloped, two had costovertebral angle tenderness, one demonstrated mild hypertension. The laboratory data as a whole were disappointing. Only 3 patients showed significant findings on examination of the urine, one demonstrated hematuria, and two had white cells in the urine.

In reviewing the histories it is apparent that the most common presenting complaint was failure to gain or underdevelopment. Negative urine is an unreliable finding on which to rule out anomalies of the urinary system. The diagnosis was apparent from the excretory urograms. The preoperative management of these patients was as follows. In addition to routine laboratory studies, blood urea nitrogen was obtained in all instances. Following excretory urography, retrograde pyelography was performed during cystoscopy. General anesthesia was administered during cystoscopy. In 3 patients preoperative ureteral peristalsis tracings were secured. Recordings were made from the lower end of

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[3] Berneike, R. R. and Deming, C. L.: Results of treatment by plastic surgical procedure with and without T tube drainage. J. Urol., 66: 68–76, 1951.

the ureter where the peristalsis is normally more active and of higher amplitude than more proximal portions of the ureter. Following the recording of ureteral peristalsis, retrograde pyelograms were made. It is advisable to delay renal exploration for 48 hours or more after cystoscopy. Unless this delay is adhered to, one may encounter acute infection in the partially obstructed kidney. It is our impression that one obtains better results when the plastic procedure is performed in an aseptic field, rather than during an acute bout of renal infection.

The operation was performed through a moderate sized, transverse flank incision. The hydronephrotic kidney was huge in size. However, it was reduced in size by aspirating fluid through a nineteen gauge needle. The ureter was identified but only dissected free at the ureteropelvic junction. At first, there seemed to be no constriction at the junction of these two structures. This was due to the fact that the stenotic portion of the ureter was concealed by tissue overlying it. We exposed the dilated pelvis; the ureter was divided 1 cm. or so below the constriction to provide an adequate lumen. The cut across the ureter was somewhat oblique to increase the circumference of the opening. A dependent point of the pelvis was selected for reimplantation. Usually, it was close to the junction of the pelvis with the renal tissue. The excess part of the pelvis was excised, and the opening was closed with a running through and through 5-0 plain catgut suture. This was reinforced with a second 5-0 chromic catgut suture which did not penetrate the pelvic mucosa. A circular opening was made at the selected point of reimplantation of the ureter. A nephrostomy tube was inserted through the renal tissue and the splint was inserted at a somewhat lower level. The anastomosis was made by placing two 5-0 chromic catgut sutures through the muscular coat of the ureter and of the pelvis adjacent to the opening. These were tied and the two structures were brought into apposition. A 5-0 plain catgut continuous suture was used to approximate the mucosa of the two structures. This was placed loosely so that the opening was not constricted, yet the two edges of mucosa were brought into perfect apposition. When about half of this suture was completed, the splint was brought down through the anastomosis into the

TABLE 1

Patient	Postop. Day Splint Removed	Pressure in Pelvis	Postop. Day Nephrostomy Removed
L.F.	Left 3rd day	9 cm. urine	10th day
D.B.	Right 4th day	8 cm. urine	7th day
	Left 4th day	8–10 cm. urine	12th day
J.P.	Left 4th day	7–8 cm. urine	38th day
E.R.	Left 5th day	20 cm. urine	3 months
G.F.	Left 7th day	9–18 cm. urine	14th day
J.P.	Left 7th day	7 cm. urine	10th day
S.V.	Right 7th day	5–9 cm. urine	9th day
B.B.	Right 9th day	20–25 cm. urine	9 weeks
J.C.	Left 9th day	20 cm. urine	30th day
J.D.	Left 9th day	0 cm. urine	12th day
D.G.	Left 11th day	12 cm. urine	24th day

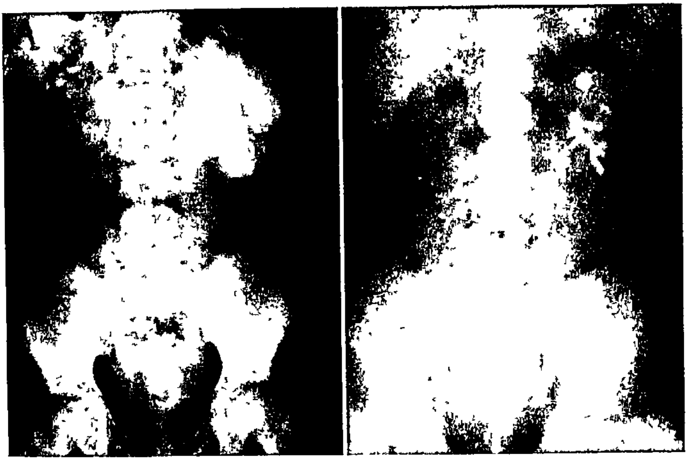

FIG. 1. Excretory urogram showing preoperative hydronephrosis on left, and result 1½ years after operation.

ureter. In all except two instances an 8 or 10F rubber catheter was used through the anastomosis. In two of the small infants these proved to be too large and a smaller polyethylene tube was used as a splint. When the splint was in place, the continuous 5-0 plain catgut suture was placed to close the remainder of the opening between the pelvic and ureteral mucosa. Two or three interrupted 5-0 chromic catgut sutures were then placed through the muscular coat to support the anastomosis. It was our practice to tack the lower pole of the kidney upward and lateral to hold the renal tissue away from the ureter. The wound was then closed without drains. Penicillin and streptomycin were administered postoperatively for four or five days. The splint was removed between the third and eleventh postoperative day, and immediately afterwards the nephrostomy tube was clamped. In 8 hours readings of intrapelvic pressure were taken. Table 1 shows the pressures found in each instance. Usually two or three readings of intrapelvic pressure were taken and if they were below 20 cm. of water pressure, the nephrostomy tube was removed. We believe that this is a physiological method of determining the function of the anastomosis, and that it is superior to direct pyelograms in appraising the function of the anastomosis.

All of the patients have been followed with postoperative x-rays (fig. 1). In 8 patients, postoperative peristalsis studies have been performed and it has been found that in most instances ureteral peristalsis is present but somewhat altered in rhythm and in amplitude (fig. 2). The rhythm is slowed from normal con-

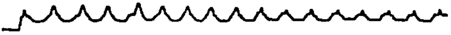

FIG. 2. Ureteral peristalsis following ureteroplasty

TABLE 2

Patient	Operation	Studies			Function			
		Pre-op.	Post-op.	No. Months Postop.	Preop.		Postop.	
					Right	Left	Right	Left
L. F.	Left	No	Yes	6 & 15 mos.	—	—	No studies	Essentially normal
D. B.	Bilateral	No	Yes	4 & 12 mos.	—	—	Normal	Normal
J. P.	Left	No	Yes	13 mos.	—	—	Normal	Slight decrease in amplitude & frequency
E R.	Left	Yes	Yes	1 & 10 mos.	No recording	Normal	Normal	Moderate decrease in amplitude & frequency
G. F.	Left	No	No	—	—	—	—	—
J. P.	Left	No	No	—	—	—	—	—
S. V.	Left	No	No	—	—	—	—	—
B. B.	Right	No	Yes	2 mos.	—	—	Decrease in amplitude & frequency	No studies
J. C.	Left	Yes	Yes	8 & 30 mos.	Normal	No recording	Decrease in frequency; slight decrease in amplitude	Low amplitude
J. D.	Left	No	Yes	3 & 10 mos.	—	—	Normal	Slight decrease in frequency & amp.
D. G.	Left	Yes	Yes	2 wks. & 10 mos.	Normal	Normal	Normal	Decrease in amplitude & frequency

tractions at 8 to 10 second intervals, to intervals of as much as 16 to 20 seconds. As these patients are followed along for several months, the rhythm approaches normal speed. The amplitude also may be somewhat diminished initially. It is our experience that a normal child has a pressure of between 35 and 40 centimeters of water with each ureteral peristaltic wave. In these patients the peristaltic pressure was slightly diminished. Again, this pressure tended to return to essentially normal levels in a matter of 6 months to a year. In one patient there was no peristalsis postoperatively. This child's ureter was large preoperatively. Unfortunately we were unable to secure preoperative peristalsis studies on this patient and it may well be that there was a congenital lesion of the ureter, and that postoperative absence of peristalsis was not entirely a complication of dividing the ureter. It would seem from these studies that division of the ureter does not abolish ureteral peristalsis, that perhaps there are minor transient changes which tend to return to normal over a period of 1 year. Table 2 summarizes these results.

All of our patients in this group have been followed for 6 months to 2 years. There has been improvement in the x-rays of the pelvis on the affected side (fig. 1). One patient, a small female, on exploration had an intrarenal pelvis with aberrant vessels which were large and attached to the lower pole of the kidney. Unfortunately, they could not be sacrificed without destroying most of the blood supply to the kidney The vessels themselves did not seem to play a role in the obstruction However, because of the aberrant vessels it was impossible to resect much of the intrarenal pelvis, and the reimplantation was difficult The patient had one bout of infection some months postoperatively, and an excretory urogram showed that the hydronephrosis was somewhat more marked than it was preoperatively It is hoped that control of the infection may yet enable us to obtain an improvement in this patient

DISCUSSION

All of our patients had ureteral implantations into the midportion of the renal pelvis Adequate treatment required division of ureter and reimplantation at the most dependent portion of the pelvis to insure adequate drainage It has been known that, experimentally, division of the ureter disturbs ureteral peristalsis This was the cause of some concern to us in considering the possible long term results on these infants and children

It occurred to us that some of the poor results reported after correction of ureteropelvic obstruction might be due to ureteral dysfunction rather than to recurrent stricture It was determined to perform ureteral peristalsis studies on our patients postoperatively to determine this point Tracings were made on 8 patients postoperatively and only minor deviations from normal were recorded This indicates that a ureter can be divided without serious damage to its function

In selecting the type of anastomosis to make we were influenced by the excellent results obtained by anastomosis utilizing mucosa-to-mucosa approximation in gastro-intestinal surgery It would seem reasonable that such a procedure would be most effective in preventing stricture in a suture line at the ureteropelvic junction A continuous suture of 5 0 plain catgut was selected for two reasons Little reaction would be produced, as this material is absorbed in a few days A continuous suture eliminated a large number of knots at the anastomosis In a small infant where structures are small, this is an important consideration Furthermore, perfect mucosa to mucosa approximation is obtained by a continuous suture

Another problem in the care of these infants which was of particular interest to us was the most effective time to remove the nephrostomy tube It is general practice to utilize direct pyelograms as an aid in making this decision A more physiological approach to this problem would be direct measurement of intrapelvic pressure and such determinations were performed on our patients From our own studies of normal intrapelvic pressure it would seem that 20 cm of water pressure can be considered the critical level After occlusion of the nephrostomy tube for 4 hours or longer, measurements of intrapelvic pressure were made utilizing spinal fluid monomanators In the majority of our patients the pressure was below 20 cm of water 10 to 14 days after operation, and the nephrostomy tubes were removed In a few instances it became necessary to maintain the tube in place for several weeks before the pelvic pressure remained normal after a test period of occlusion. Our explanation of this delay in adequate anastomosis function was infection and edema at the suture line.

CONCLUSION

Measurement of intrapelvic pressure with a nephrostomy tube is an excellent method of determining the function of the anastomosis after ureteropelvic strictures have been excised.

Division of the ureter does not destroy ureteral peristalsis. There are minor changes which tend to correct themselves with the passage of time.

A technique of mucosa-to-mucosa approximation has proved quite effective and in 10 cases out of eleven, there has been marked improvement in the degree of hydronephrosis.

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HAMARTOMA OF KIDNEY

KEN MOONEY

Hamartoma may be defined as the overdevelopment of some tissue element which belongs normally at the site where it is found, or to abnormal relationship of a normally situated tissue element

Renal hamartoma has been recently very thoroughly covered by Hulse and Palik Hamartoma of the kidney is a relatively rare surgical finding and may occur as an isolated entity as in this case, or as a part of the tuberous sclerosis complex described by Moolten

Hamartoma arising from the pelvis of the kidney is still a more rare surgical finding, and as far as I have been able to find, only one other case has been reported in the American literature This case was reported in the case records of the Massachusetts General Hospital (No 35221, June 2, 1949)

The tuberous sclerosis complex is made up of three types of lesions a) brain lesions designated as tuberous sclerosis, b) skin lesions, the most common of which is adenoma sebaceum, and c) visceral lesions, which so far have been found in heart, liver, spleen, bone and kidney

CASE REPORT

Mrs J V B , a white married woman, aged 44, was referred to my office, complaining of frequency, nocturia and dysuria of 1 week's duration On April 9, 1954, two days after symptoms had begun, the patient had gross hematuria, associated with left flank pain and temperature of 100F In the past, she had attacks of frequency, nocturia and disuria, but never as severe as in the present attack

Two years previously she had had an attack of gross, painless, total hematuria and was advised by her family physician to see a urologist, but she failed to do so and had had no recurrence until the onset of the present illness An inventory by systems revealed that she had been a relatively healthy individual throughout her entire life She had borne two boys, one 22 and one 11 years of age There were no renal complications during either pregnancy

The patient was not acutely ill Tenderness was elicited over the left renal area, the lower pole of the left kidney could be palpated, and the lower pole was thought to be normal in size Remainder of the physical examination was noncontributory

Urinalysis Specific gravity, 1 005, albumin, negative, sugar, negative, microscopic examination, 25 to 30 white blood cells per high power field

A plain x-ray (fig 1, *A*) showed that the right kidney was very well outlined and normal in size and position The left kidney was not outlined so well and there were some large phleboliths noted in the right true pelvis

The first excretory urograms taken 8 minutes after intravenous injection of 20 cc of diodrast (fig 1, *B*) showed the right kidney normal in size and position and with excellent function The left kidney was slightly enlarged and three,

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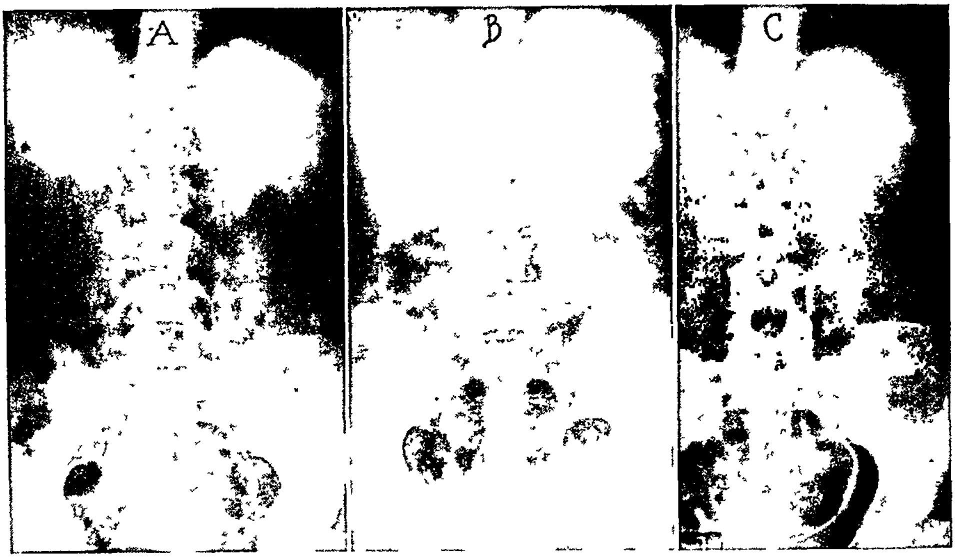

Fig. 1

possibly four, large blobs of the dye were noted, which were assumed to represent the calyces of the left kidney. On the 15 minute film, there was a large amount of the dye seen in the bladder. There were still three large blobs of the dye representing the calyces of the left kidney which were dilated and blunted. The left kidney itself was not outlined; neither was any portion of the right nor the left ureter.

It was decided that the patient should be hospitalized and that cystoscopy and left retrograde pyelography should be performed under anesthesia. The patient was admitted to Baylor University Hospital, Dallas, Texas on April 15, 1954 (case MM-99810).

Laboratory findings were: Hemoglobin, 12.1; red blood cells 4,110,000; white blood cells 5,900 with a normal differential; clotting time 4′44″; hematocrit 39. A second urinalysis revealed: Specific gravity, 1.005; reaction acid; albumin 300 mg. per cent; sugar, acetone and diacetic acid, negative; appearance, grossly bloody; blood urea, 34; urea nitrogen, 16; culture of urine from left kidney, Alcaligines faecalis.

A size 24 panendoscope sheath was passed easily through the urethra and a complete inspection of the mucosa of the bladder and urethra was carried out. Mild granular urethritis was present; the bladder mucosa everywhere was found to be normal; there were one right and one left ureteral orifice. This instrument was removed and a No. 16 Brown-Buerger instrument passed into the bladder. A No. 5 catheter was passed 18 cm. up the left ureter where complete obstruction was met. Only a few drops of urine came through the catheter. This contained grade 3 pus.

Skiodan (15 cc) was injected (fig. 1, *C*). The film showed that none of the skiodan reached the kidney. There was kinking in the upper third of the left ureter, and also an irregular filling defect just above the second kink. A second attempt was made to get dye into the kidney pelvis, but with no success.

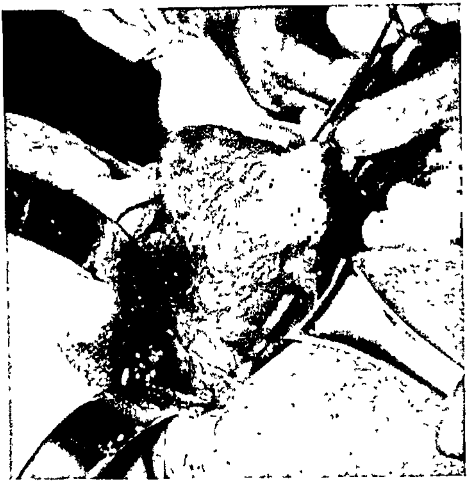

Fig. 2

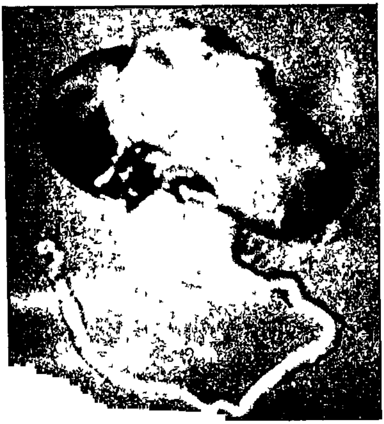

Fig. 3

The diagnosis was tumor involving the upper third of the left ureter and possibly the kidney pelvis.

On April 19, 1954, under general anesthesia, a left nephroureterectomy, with a cuff of the bladder removed, was performed. Figure 2 shows exposure of the upper ureter and kidney. No complication was encountered. Figure 3 shows the kidney and ureter intact, and figure 4 shows the kidney and upper ureter open.

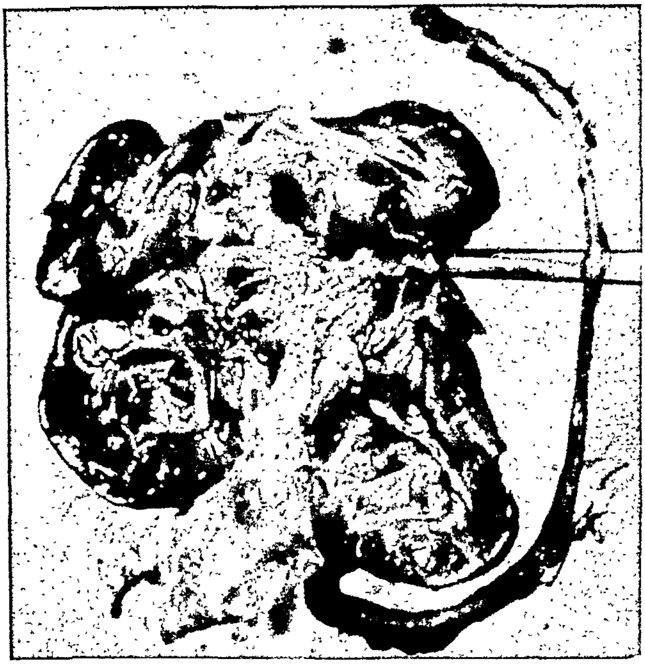

FIG. 4

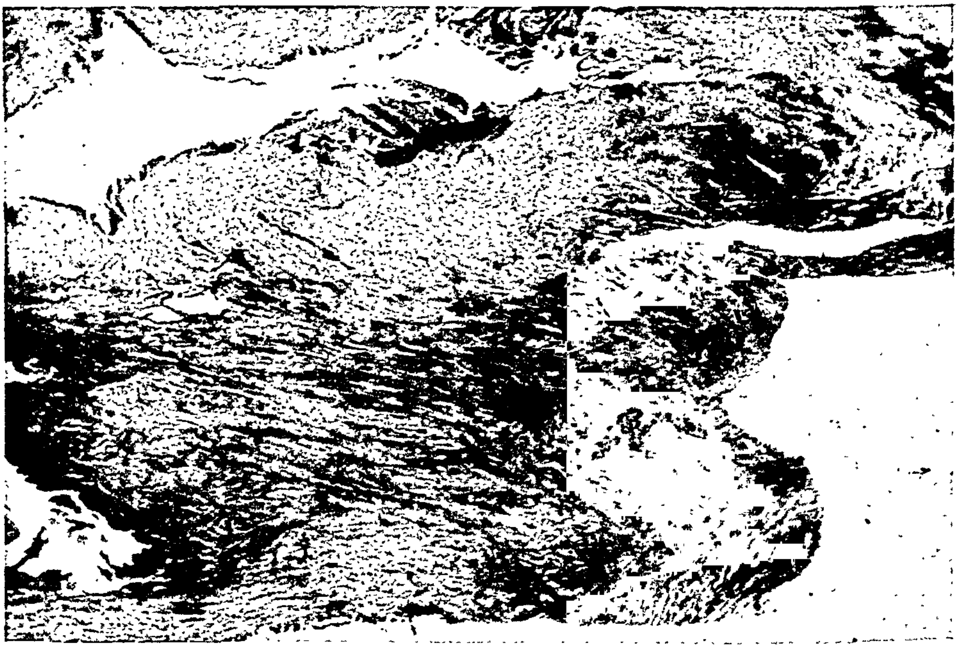

FIG. 5

Pathological report (Dr. C. E. Gordon): The kidney and ureter weighed 150 gm. and measured 11 by 5 by 5.5 cm. The ureter was 22 cm. long. It appeared grossly normal. On opening the kidney, there appeared a polypoid structure extending into and filling the pelvis and having its pedunculated attachment to the mucosa of the middle major calyx. The pedicle was 8 cm. long and the cystic-like mass at the lower end (fig 4) measured 3 cm in its broadest diameter The capsule of the kidney stripped with ease, and the underlying parenchyma was smooth and had a greyish-brown appearance The cortex varied in thickness from 1 1 cm at the superior and inferior calyces to 0 4 cm at the middle major calyx In this area the parenchyma was atrophic

On microscopic examination (fig 5), the surface of the polypoid mass was covered with a well differentiated transitional cell epithelium The stroma consisted of fairly dense connective tissue throughout, in which were bundles of smooth muscle fibers Throughout were many cysts of varying size, which were lined by a low columnar to cuboidal epithelium Beneath the surface epithelium, there was an inflammatory exudate composed chiefly of plasma cells In some areas, the connective tissue was highly vascular, the blood vessels being largely of venous and capillary type

Sections of the adjacent kidney showed focal accumulations of inflammatory cells of chiefly lymphocyte type in the cortex Occasional hyalinized glomeruli were noted and occasional glomeruli showed periglomerular fibrosis

Sections were reviewed by the Armed Forces Institute of Pathology, and the term "cystic malformation" was applied

COMMENT

This case was extremely interesting to me because of its rareness I was very happy to find a nonmalignant lesion No deep x-ray therapy was given At the present time, the patient is enjoying excellent health and no further symptoms have been noted

CONCLUSION

The second case of hamartoma arising from the renal pelvis has been reported This case has no relationship to the tuberous sclerosis complex

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THORACOABDOMINAL NEPHRECTOMY IN THE LARGE, FIXED INFECTED KIDNEY

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In urology the thoracoabdominal approach is restricted to a limited field. It is used for large renal tumors, cysts, adrenal tumors and for retroperitoneal gland dissection in testis tumors. We have used it 6 times in 5 cases of large chronic calculus pyelonephritis or pyonephrosis, with excellent results. In three of the cases nephrectomy by the usual lumbar incision has been attempted; these attempts were unsuccessful because of hemorrhage and shock, dense adhesions or the large size of the renal mass.

Five cases are too few to be of numerical importance or statistical value, but it is believed that the satisfactory end results and experience gained are of sufficient value to warrant a report.

The thoracoabdominal incision is not advocated as a routine approach in all cases of chronic calculus pyelonephritis or pyonephrosis but only in those cases that offer the prospect of the most difficult and at times impossible nephrectomy. The ideal incisions for this type of case must meet the following requirements: 1) excellent exposure; 2) early and easy ligation of the renal vein and artery; 3) reduction of trauma and blood loss to prevent shock; 4) prevention or reduction of injuries to other organs, the aorta and vena cava. The thoracoabdominal incision meets these requirements. An incision that fails to meet them does not offer the lowest rate in morbidity and mortality.

The worry of empyema and peritonitis from this approach in the infected kidney has been overemphasized. There was a spill of pus into the operative field in five of the 6 operations, in most instances from a perirenal encapsulated pocket of pus. Infection was a problem in only one case and was due to failure to remove the kidney and the attempt to drain it with a nephrostomy tube. With the aid of antibiotics, infection of these cavities usually does not occur from one gross contamination but from repeated leaks of infection.

CASE REPORTS

Case 1. J. K., a 33 year old white man, had incomplete paralysis of the lower extremities from fracture of the second lumbar vertebra in 1945. At this time there were also multiple fractures of the long bones. Many mistakes were made in the management of the case and the experience gained from them will be of value in the handling of future cases of this type.

In March 1946 a staghorn calculus developed in the right kidney (fig. 1, *B*). In 1949 a calculus measuring 6.5 by 5 cm. was removed from the prostatic

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Read at annual meeting, Southeastern Section of American Urological Association, Palm Beach, Fla. April 12–15, 1954.

A detailed account is available in Transactions of Southeastern Section, 1954, pp. 41–50.

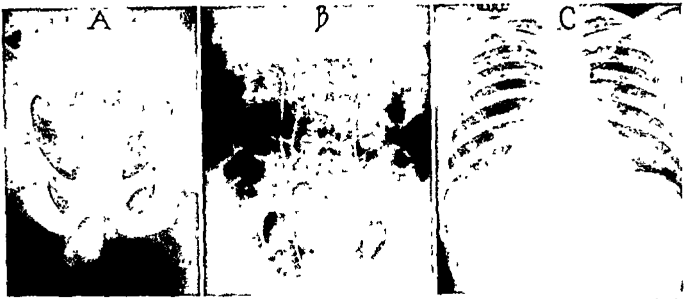

FIG. 1. Case 1. *A*, stone in prostatic urethra. *B*, stone in right kidney. *C*, x-ray of chest after first thoraco-abdominal operation.

urethra (fig. 1, *A*) by the retropubic approach. All of the stone was in the prostatic urethra and the urine was voided around it.

In July 1949 an attempt was made to remove the kidney through a lumbar incision but was unsuccessful because of the size of the renal mass, the dense adhesions, hemorrhage and shock. In addition to this, a perinephric abscess was encountered. An attempt was made to insert a nephrostomy tube (intrarenal pelvis) but the tube failed to drain and had to be removed. This left the patient with a sinus tract that drained pus and urine. There were repeated attacks of chills and fever following this operation.

In April 1950 an attempt was made to remove the kidney by a thoracoabdominal incision. The tenth rib was resected, the pleural cavity opened and the incision extended to the umbilicus opening the abdominal cavity. Adhesions between the parietal and visceral pleura were separated by sharp dissection. There was a large mass in the right upper quadrant of the abdomen, composed of the bowels and liver that were adherent to the renal mass and diaphragm by dense fibrous adhesions. At the time of the injury there had probably been perirenal, intra-abdominal and intrapleural hemorrhage, from injury of the kidney, liver and chest.

With difficulty the mass was separated from the diaphragm by sharp dissection. The diaphragm was then incised in line with the chest incision. In attempting to free the liver and bowel from the renal mass a large laceration was made in the liver. Four pints of blood were given but the operation had to be discontinued because of hemorrhage from the lacerated liver and shock. The laceration in the liver was packed with oxycel gauze.

Again an attempt was made to place a nephrostomy tube for drainage; the kidney pelvis was intrarenal and it functioned poorly. In closing the incision it was found to be impossible to close the abdominal cavity to prevent leakage into it from the nephrostomy tube. The portion of the kidney through which the nephrostomy tube passed was sutured to the abdominal wall. Drains were placed to the laceration in the liver. A flanged dePezzer catheter was passed through a stab wound in the interspace above the resected rib. The diaphragm, abdominal and chest incisions were closed in the usual manner.

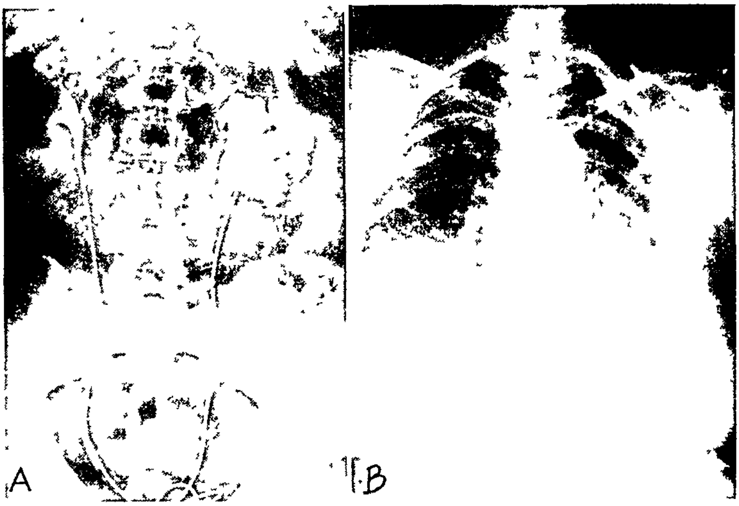

FIG. 2. Case 2. *A*, left pyonephrosis. *B*, x-ray of chest, fourth postoperative day

The postoperative course was stormy for the first week. The temperature was 103F the first postoperative day and normal by the seventh. Abdominal distention required the use of a Wangensteen suction tube. The chest catheter was removed on the second postoperative day. A chest x-ray on the fourth day revealed no evidence of fluid or pneumothorax (fig. 1, *C*). Jaundice developed on the eighth postoperative day. On the sixteenth postoperative day 75 cc pus was aspirated from either the chest or a subdiaphragmatic abscess. The nephrostomy tube functioned poorly and was removed on the ninteenth postoperative day.

This operation failed because an attempt was made to free the kidney before locating and ligating the renal pedicle. By dissection through the adherent bowels and securing the renal pedicle, a subcapsular nephrectomy could have been done.

In June 1951 a successful thoracoabdominal nephrectomy was performed. The bowel adhesions were separated and the renal artery and vein ligated. A subcapsular nephrectomy was done without hemorrhage. The capsule was closed and drained through a stab wound in the loin. The temperature was 103F on the first postoperative day. On the third day the temperature was normal and the chest catheter was removed. The remainder of the hospital stay was uneventful.

Anemia was present before operation and 2500 cc blood was given before, during and after the operation.

The incision healed rapidly and the patient has been free of acute episodes of urinary tract infection since the operation.

Case 2.[1] B. E. R., a 49 year old white woman, was admitted to the hospital on January 7, 1950, with a history of having passed two small calculi 7 years previously, and an attempted left lumbar nephrectomy 2 years previously. She had had persistent left flank pain for the past 5 years, with gross hematuria, chills and fever at frequent intervals.

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[1] Previously reported: Robertson, J. P. and Jameson, Samuel: Thoracoabdominal nephrectomy. J. Urol , **67**: 585–597, 1952.

The physical examination was negative except for obesity and tenderness over the left abdomen and flank

Cystoscopy revealed chronic cystitis with toothpaste-like pus exuding from the left ureteral orifice There was normal excretion of indigo carmine from the right kidney and none from the left The retrograde pyelograms revealed a normal right kidney and a large left pyonephrotic sac (fig 2, *A*) There were no shadows to indicate stones The bladder urine and left kidney urine were loaded with pus and gram-positive cocci and gram-negative bacilli The urine from the right kidney was negative for pus and organisms

The urologist who attempted the nephrectomy reported that due to marked perirenal adhesions, the patient's short stature and obesity, he did not believe that the kidney could be removed by a lumbar incision With this advance information, it was decided that the thoracoabdominal approach would be the safest and easiest for the patient A catheter was left indwelling to the left kidney for 3 days, during which time sulfadiazine, penicillin and streptomycin were given

On January 10, 1950, using sodium pentothal and intratracheal ether and oxygen anesthesia, a left thoracoabdominal nephrectomy was performed The line of incision was over the tenth rib and downward and across the abdomen The tenth rib was resected subperiosteally near the spine The diaphragm was opened in line with the incision The renal vein and artery were dissected out and individually clamped and ligated The ureter was isolated, clamped and ligated The kidney was then freed, much of it by sharp dissection. In the area of the renal pelvis an encapsulated perinephric abscess was opened that burrowed into the psoas muscle A stab wound was made in the flank and two rubber drains left in the renal fossa The peritoneum was closed with interrupted sutures to cover the renal fossa and return the bowel to its normal position Two dePezzer

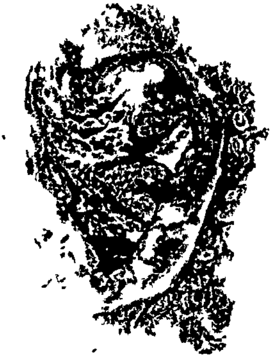

FIG 3 Case 2 Kidney bisected Note scar tissue surrounding kidney

catheters were left in the pleural cavity. The condition of the patient was excellent throughout the procedure. Blood (1000 cc) was given during the operation.

The postoperative course was uncomplicated, except for moderate abdominal distention for the first 48 hours. Penicillin and streptomycin were given for the first 4 days, and the highest temperature was 100.4F. Seventy-two hours after surgery, an x-ray of the chest (fig. 2, *B*) revealed complete re-expansion of the lung and the dePezzer catheters were removed. On the fifteenth postoperative day, the patient was discharged with the incision healed (fig. 4) and asymptomatic.

The microscopic diagnosis was 1) "chronic pyelonephritis with fibrosis; 2) squamous metaplasia of renal pelvis and calyces; 3) adenoma of renal parenchyma, benign" (fig. 3).

Case 3. J. S., a 35 year old Negro, was seen September 10, 1952 with a history of pain in the left renal area of 2 years' duration. At cystoscopy elsewhere 4 months previously a catheter would pass only 4 cm. up the left ureter. The drainage from the left catheter was purulent and clear from the right. Two months later, the left ureteral orifice could not be identified.

FIG. 4. Case 2. Healed incision

In July 1953 a lumbar nephrectomy was attempted by a competent urologist, but was unsuccessful because of the size of the kidney and the dense adhesions.

On September 15, 1953, by means of a left thoracoabdominal approach, the chest cavity was entered through the ninth interspace, the abdominal incision extended to the umbilicus. A large renal mass 6 by 9 inches was encountered. It was densely adherent to the bowel, spleen, and diaphragm. The diaphragm was freed from the renal mass, bowel, and spleen, and opened in line with the incision. The renal vein and artery were located and individually ligated. The ureter was greatly dilated and thickened. Some calcification was noted in cutting across it. The renal mass was then removed by sharp dissection. Several pockets of purulent material were encountered during the dissection.

The renal cavity was drained through a stab wound in the loin and the peritoneum was closed to cover the renal bed. The pleural cavity was drained through a stab wound in the interspace above and below the incision with a dePezzer catheter. The blood pressure was stable and patient's general condition good throughout the procedure. He received 1000 cc of blood during the operation.

The postoperative course was excellent. The temperature was 102F the day before the operation, 101F the first postoperative day, and normal on the fourth postoperative day. Wangensteen suction was employed the first postoperative day. On the second postoperative day, the abdomen was flat, the Wangensteen

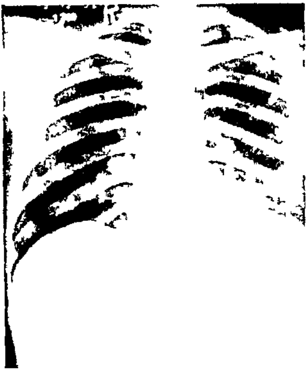

FIG 5 Case 3 X ray of chest, fourth postoperative day

suction was discontinued and the chest catheters removed An x-ray of the chest is reproduced in figure 5 On this day he was able to sit on the side of the bed, and was taking fluids freely

The pathological diagnosis was "tuberculous pyelonephritis with secondary pyonephrosis, tuberculous ureteritis" The patient was placed on streptomycin, 1 gm twice a week and para aminosalicylic acid, 2 gm, 4 times a day His weight at operation was 132 pounds In 9 months it had increased 235 pounds When last seen, 15 months following operation, he had reduced to 185 pounds The urine was negative for pus, sugar and albumin Gram and acid-fast stains of urine were negative for organisms and pus Excretory urography revealed a normal urinary tract on the right side

Case 4 E E, a 37 year old Negress, gave a history of pain and a mass in the left renal area of 7 months' duration, accompanied by chills and fever The blood pressure had been elevated for the past year A large, firm, smooth, tender mass

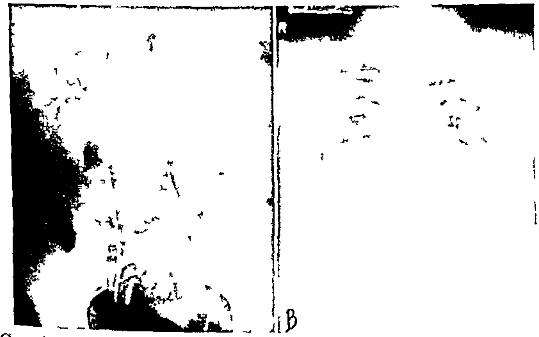

FIG 6 Case 4 *A*, left pyonephrosis with calculi *B* X ray of chest, second postoperative day

filled the left upper quadrant of the abdomen. Retrograde pyelograms revealed a normal right kidney and a nonfunctioning left kidney, with calculi filling the pelvis (fig. 6, *A*). Because of the extreme obesity of the patient and the large size of the mass, the thoracoabdominal approach was the procedure of choice.

April 3, 1951, a left thoracoabdominal nephrectomy was performed. The tenth rib was resected. The renal mass was densely adherent and was freed by sharp dissection. During dissection, an abscess pocket was opened and pus drained into the abdominal field. The renal mass measured 20 by 15 by 10 cm. The pleural cavity was drained through the seventh interspace with a flanged de Pezzer catheter, the renal cavity through a stab wound in the flank. The diaphragm, abdominal and chest incisions were closed in the usual manner. The temperature was 102F the first postoperative day, and normal on the second. The chest catheter was removed on the second postoperative day (fig. 6, *B*) and by the third postoperative day the patient was able to be up. She was discharged with the lung fields clear and the incision healed on the eleventh postoperative day.

The pathological diagnosis was "renal calculi and pyonephrosis."

Case 5. M. B., a Negress aged 38, gave a history of a mass in the left upper quadrant of the abdomen that had increased in size for the past 6 months. During this time, she had had chills and fever and on several occasions hematuria had been noted.

A large, firm, tender, slightly movable mass filled the left upper quadrant of the abdomen.

Cystoscopy and retrograde pyelograms revealed a normal right kidney with good function, a nonfunctioning left kidney that contained two large calculi in the renal pelvis (fig. 7, *A*). A large tumor mass filled the upper quadrant of the abdomen. The preoperative diagnosis was left calculous pyonephrosis and a large renal mass.

Due to the large size of the renal mass, it was believed that the thoraco-

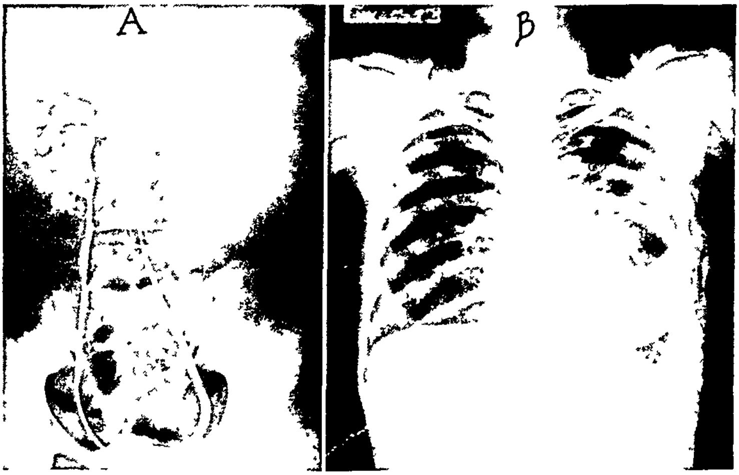

FIG. 7. Case 5. *A*, left chronic suppurative pyelonephritis with calculi. *B*, x-ray of chest, second postoperative day. Note collection of fluid.

abdominal approach offered the prospect of the easiest nephrectomy The patient was anemic and received 2000 cc of blood before surgery

Employing intratracheal anesthesia on July 22, 1952, a left thoracoabdominal nephrectomy was performed The ninth rib was resected The spleen was densely adherent to the renal mass and was removed The renal mass was freed from the surrounding structures The ureter was separated from the other structures, divided and ligated The renal pedicle was isolated, clamped, divided and ligated and the kidney removed by blunt and sharp dissection The pleural cavity was drained through the eighth interspace with a flanged dePezzer catheter and the renal cavity through a stab wound in the loin The peritoneum was closed to cover the renal bed The incisions were closed in the usual manner Blood (1500 cc) was given during the operation The pleural catheter was removed on the second postoperative day (fig 7, *B*) and the patient was up in a chair The temperature was 101 5F on the first postoperative day, and 99F by the second day Convalescence was uneventful except for a collection of fluid in the chest that absorbed without aspiration The patient was discharged on the eighth postoperative day

Pathological diagnosis "Chronic suppurative pyelonephritis with calculi" The renal mass measured 20 by 10 by 10 cm

Five cases of large, infected, densely adherent kidneys were removed by the thoracoabdominal approach in 6 operations Two operations were done by the house staff and four by the author

In 5 cases, pus was spilled into the operative field One case of questionable infection of the chest occurred This was in case 1, where the kidney was not removed and drainage was attempted by a nephrostomy tube that failed to function The author believes that the danger of peritonitis and empyema has been over emphasized

The advantages and disadvantages of the operation have been stressed

In three of the cases, lumbar nephrectomy had been attempted, but was unsuccessful because of dense adhesions, large size of renal mass and hemorrhage The final results in the 5 cases were good

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CONCURRENT DISSIMILAR MALIGNANCIES OF THE URINARY TRACT

DAVID W. KLINE, MATTHEW MARSHALL, JR., S. HARRIS JOHNSON, III AND GLENN REED

The finding of concurrent, dissimilar malignancies of the urinary tract is thought to be rare enough to warrant reporting. A search of the literature shows a rather large selection of multiple papillary tumors that are found from the renal papillas to the urethral meatus. Fewer articles deal with unrelated malignancies in the same individual at different times. There are only a few reports of different histologic tumors of the urinary tract occurring simultaneously. We are presenting 2 cases of dissimilar malignancies of the urinary tract occurring simultaneously.

CASE REPORTS

Case 1. E. L. C., Sharon General Hospital No. 177061, aged 54, was admitted February 18, 1952 with hematuria of 2 days' duration. Transient hematuria occurred in 1949. The lower pole of the right kidney was palpable. A urinalysis confirmed the history of hematuria, but other laboratory examinations were not abnormal. Excretory urography visualized a normal left kidney, but the right kidney contained a mass 9.0 cm. in diameter in the lower pole which distorted the adjacent calyces. A chest film showed no metastasis. Cystoscopy visualized a pedunculated papilloma, 4.0 cm. in diameter, adjacent to the left ureteral orifice. This was resected transurethrally and the patient made an uneventful recovery. Nine weeks later right nephrectomy and subtotal ureterectomy were performed. The perirenal fat and fascia and the lymph nodes at the renal pedicle were removed with the specimen and grossly the tumor did not appear to extend beyond the specimen. Convalescence was uncomplicated.

Grossly the bladder fragments were gray-red. Microscopically, there were many papillary processes covered by stratified transitional epithelium. The cells showed variation in nuclear size, some prominent nucleoli and occasional mitotic figures. Fragments of smooth muscle were present and showed no invasion by tumor. The diagnosis was low grade papillary carcinoma.

Cross section of the kidney exposed a well circumscribed tumor. It was red-gray, soft, and measured 7.5 cm. in diameter. It did not invade the pelvis. Microscopic sections showed misshapen tubules lined by multiple or single cell layers. The cells were polyhedral, had eosinophilic cytoplasm and small dark nuclei. There was no penetration of the pelvis and little invasion of the surrounding parenchyma. The diagnosis was granular cell adenocarcinoma of the kidney. See figure 1.

Case 2. W. F. D., Western Pennsylvania Hospital, No. 3612, aged 47, entered the hospital with a 4-month-history of hematuria, dysuria and frequency. Physical examination revealed no urologic abnormalities. A urinalysis revealed albuminuria, hematuria and pyuria. Urine culture demonstrated Pseudomonas aeruginosa. The patient was anemic but other laboratory determinations were

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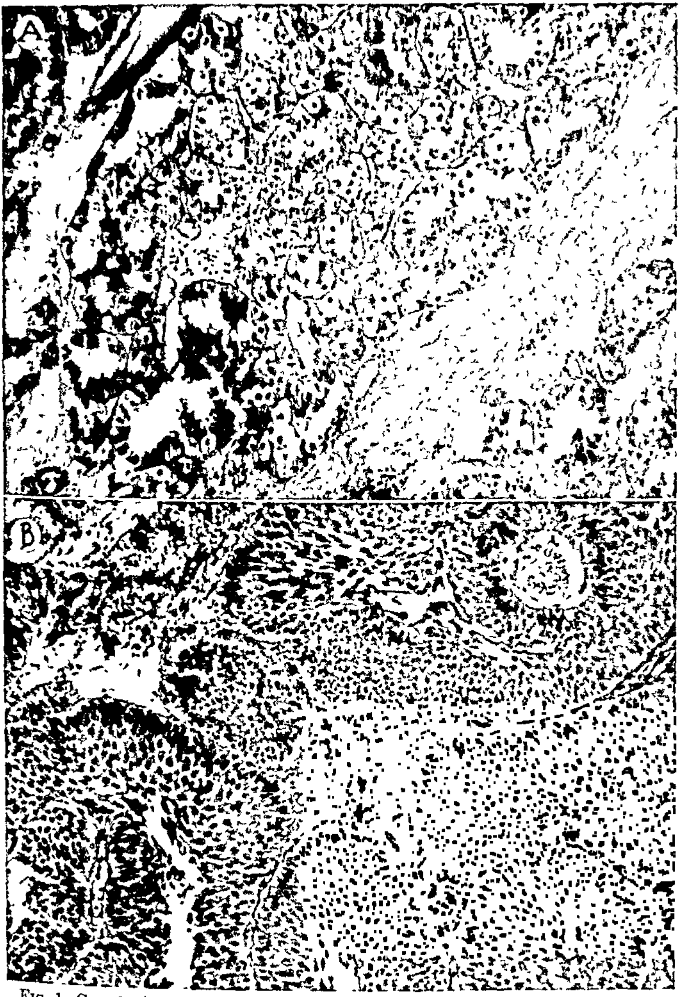

Fig. 1. Case 1. *A*, papillary carcinoma of bladder. *B*, adenocarcinoma of kidney.

within normal limits. Excretory urography visualized a normal right kidney, but the exact renal outline on the left could not be determined and the calyces, while demonstrating marked dilatation, were poorly filled. A chest film showed no metastasis. Cystoscopy visualized a papillary tumor overlying the left ureteral

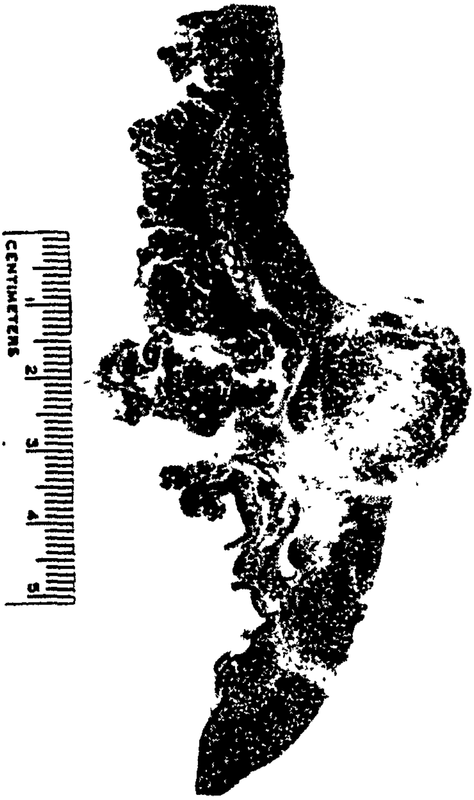

FIG. 2. Case 2. Cross section of kidney showing papillary carcinoma and adenocarcinoma.

orifice. Left hemicystectomy, neoureterocystostomy and pelvic lymphadenectomy were performed and no gross evidence of metastasis was encountered. A cystostomy tube and left ureteral catheter were left indwelling. Postoperatively a pyelogram was performed by injection of radiopaque dye into the ureteral catheter and this demonstrated a reduplicated renal pelvis and partial reduplication of the ureter. A filling defect was present in the upper renal pelvis. A left nephroureterectomy with removal of the perirenal fat and fascia and the lymph nodes at the renal pedicle was performed and the patient made an uneventful recovery.

Pathological report: A pedunculated, papillary tumor, 2.0 cm. in diameter, arose from the mucosal surface of the bladder and was penetrated by the ureter. Normal bladder surrounded the tumor mass. Six lymph nodes were received and appeared normal. Microscopically, a low papillary tumor arose from the mucosal surface. The tumor cells pierced the basement membrane at some points. The nuclei were pleomorphic and occasionally giant. A transitional epithelial pattern was preserved and invaded the muscularis superfically. The diagnosis was transitional cell carcinoma.

Cross section of the kidney revealed a papillary mass, 6.0 cm. in diameter,

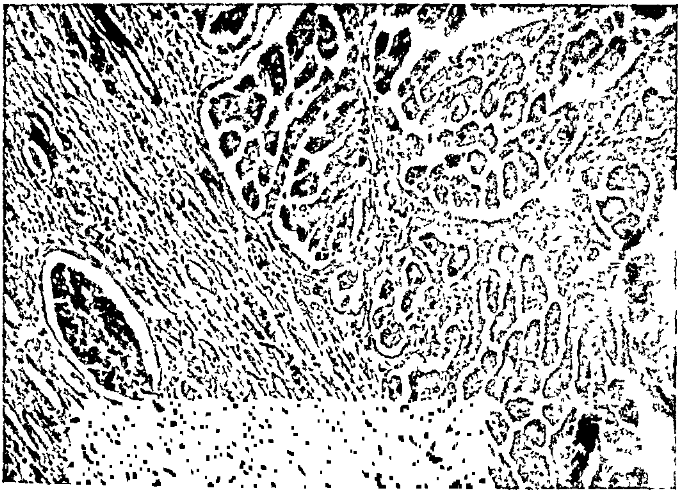

FIG. 3. Case 2. *A*, papillary carcinoma of bladder. *B*, papillary carcinoma of kidney.

arising from the kidney pelvis and invading the parenchyma. A smaller subcortical tumor in the lower pole was separated from the first tumor by a thin zone of preserved parenchyma. It appeared encapsulated and was solid, firm and yellow-red. Microscopically, the epithelial tumor in the upper renal pelvis was almost identical with the bladder tumor but was more invasive. The parenchymal tumor was imperfectly encapsulated and had a different histologic pattern. Superfically the tumor seemed solid but consisted of intricate papillary processes. These were lined by anaplastic cuboidal or low columnar epithelium and supported by slim bands of stroma. The nuclei were relatively large and the cystoplasm granular and eosinophilic. The diagnosis was papillary transitional cell carcinoma of the renal pelvis and papillary renal cell adenocarcinoma. See figures 2, 3, 4.

COMMENT

While there are earlier reports of multiple dissimilar tumors of the urinary tract, Graves and Templeton first presented a well documented report of dissimilar tumors in the same kidney in 1921. The simultaneous occurrence of similar multiple tumors of the urothelium has been stressed, but the cases reported by us, as well as our review of the literature, would indicate that dissimilar tumors may also occur. The tendency for any cancer patient to develop another primary tumor is a factor that must be considered in the treatment of the individual patient.

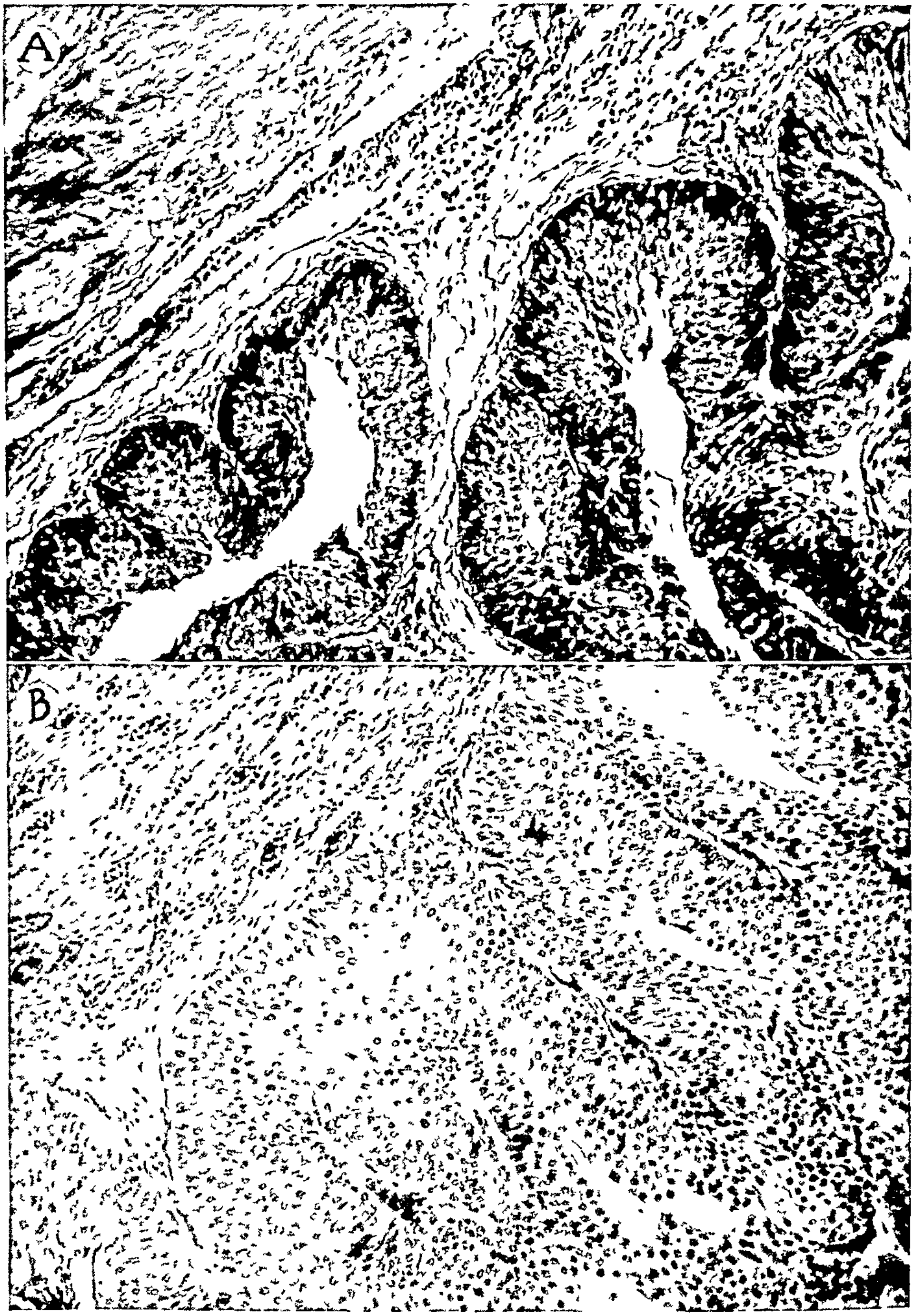

Fig 4 Case 2 Adenocarcinoma of kidney

SUMMARY

Two case reports of dissimilar malignancies of the urinary tract are presented. Case 1 demonstrated a simultaneous papillary carcinoma of the bladder and adenocarcinoma of the kidney Case 2 demonstrated the simultaneous occurrence of a transitional cell carcinoma of the bladder in association with a similar tumor in the upper pole of a fused double kidney and an adenocarcinoma in the lower component of the same kidney

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A STUDY OF THE ELECTRICAL ACTIVITY OF INTACT AND PARTIALLY MOBILIZED HUMAN URETERS

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Studies of the ureter have been carried out by many investigators using a variety of techniques, yet many clinical and physiologic problems remain to be solved. This investigation of ureteral electrical phenomena was undertaken to develop a method of studying ureteral activity which might be used in both man and animals to learn more of ureteral function during health and illness, and particularly to study hydronephrosis. That mechanical obstruction alone is not the cause of all hydronephrosis in man is indicated by the fact that hydroureter and hydronephrosis are not always associated with demonstrable mechanical obstruction of the ureter. In fact, complete acute ureteral obstruction is not followed by progressive hydronephrosis; congenital megaloureter occurs without demonstrable anatomic obstruction; and hydronephrosis develops rapidly in some cases of ureteral transplantation without definite anatomic stricture or stenosis subsequently being demonstrated. Hydronephrosis also may develop after ureteral transplantation only to disappear gradually during succeeding months.[1] The postulation of edema and/or stricture does not explain adequately this phenomenon.

METHOD

The patients whose ureters were investigated were mainly those in whom ileal bladder substitution (with or without pelvic evisceration) was contemplated and in whom excretory urography revealed no appreciable ureteropelvic dilatation. A few other patients undergoing cystoscopy and/or retrograde pyelography for diagnostic purposes also were studied if the renal collecting systems appeared roentgenographically normal. A total of 17 patients have been investigated. Records satisfactory for interpretation were obtained in twelve of them.

At preoperative cystoscopy, a No. 4 to 6 ureteral catheter with attached silver wire electrodes was inserted into the lower one third of the ureter (fig. 1). The electrode leads then were attached to a standard clinical electrocardiograph (EKG) machine so that a voltage increase at the electrode nearest the kidney produced a positive deflection on the record. (See figure 1 for details of the electrode-catheter construction.)

In the 6 patients subjected to ileal bladder substitution, the ureteral catheter with attached silver wire electrodes was used in preoperative study where feasible,* but a specially constructed electrode assembly was left in the ureter at operation to study postoperative ureteral function (fig. 2). After positioning of

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[1] Bricker, E. M., Butcher, H. and McAfee, C. A.: Late results of bladder substitution with isolated ileal segments. Surg., Gynec. & Obst., **99**: 469–482, 1954.

* Often the extent of tumor involvement and/or the presence of a large vesicovaginal fistula will preclude cystoscopic visualization of the ureteral orifices.

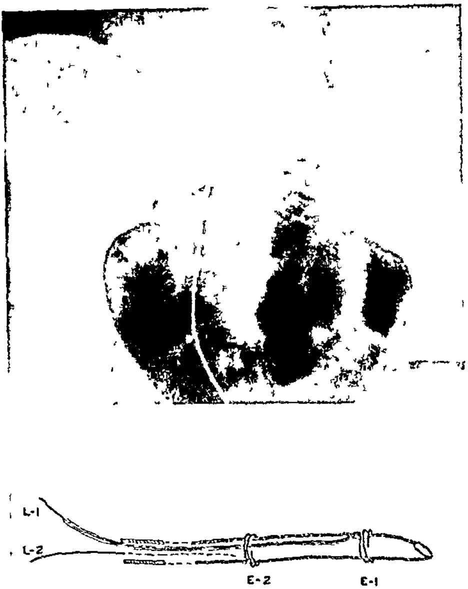

FIG. 1. Roentgenogram shows ureteral catheter with attached electrodes placed in lower portion of ureter Diagram shows method used to construct this bipolar recording unit. Two silver wires, 0 01 inches in diameter, were passed through catheter lumen and brought to its outer surface 30 mm. apart. Two to three closely approximated turns of uninsulated silver wire acted as electrodes. Stretched polyethylene tubing (0 04 inches in diameter) was used to insulate one lead from other within catheter lumen. If ureteral catheter used was smaller than No. 6, it was necessary to lead one insulated silver wire along outside of ureteral catheter.

the electrodes in the ureter during the operation the leads were brought through the ureteroileal anastomosis and the ileal segment, then attached to the skin.

At the time of the cystoscopic studies, the two intraluminal electrodes were in the lower one-third of the ureter (fig. 1). The assembly left in the ureter at operation was positioned so that the upper two electrodes were in the upper undisturbed segment, while the lower two electrodes were left in the distal mobilized segment of the ureter (fig. 2). Silver clips were used in 3 patients to mark the extent of mobilization of the ureter, so that the electrode position in relation to this area of ureter could be determined by x-ray during the postoperative period of study. No shifts in electrode positions were noted. The intact ureter was studied in 2 patients during operation. Immediately after nephrectomy in one patient, a small balloon attached to a polyethylene tube (0.04″ to 0.07″ in diameter) was inserted into the upper ureteral lumen; and by its distension, peristaltic waves were stimulated. These waves were recorded from electrodes attached to a ureteral catheter and inserted into the lower third of the ureter preoperatively.

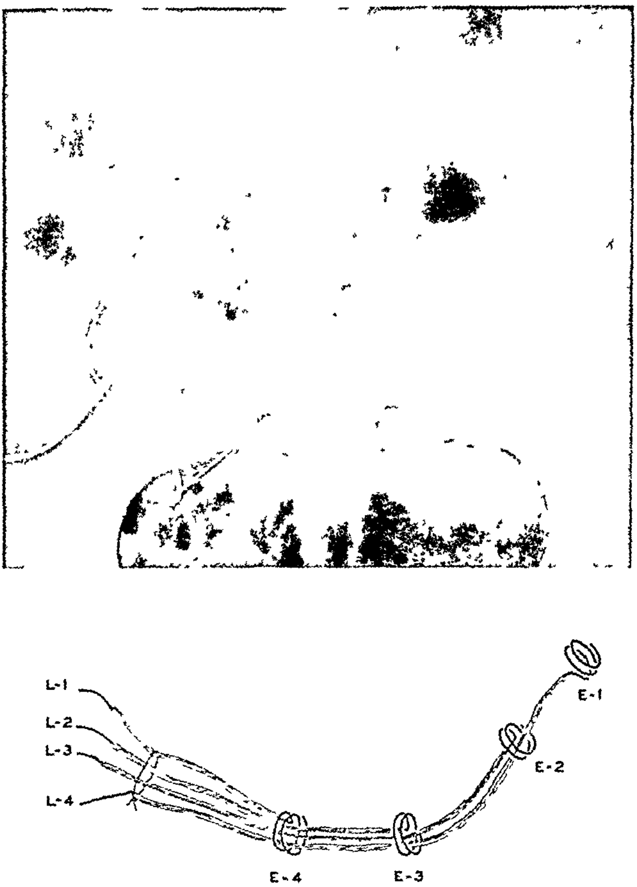

FIG. 2. Roentgenogram above shows electrode assembly within ureter as placed during operation. Construction of this assembly is shown on diagram. Silver wires (0.01 inches in diameter) with polyethylene tubing stretched over them as insulation, made up leads; electrodes were uninsulated, coiled end of each lead Insulated leads were tied together so that interelectrode distances remained constant.

In the other patient studied during the operative procedure, the electrodes and stimulating balloon were inserted upward from the cut end of the right ureter and recordings taken before ureteroileostomy was completed.

An understanding of the fundamental electrical nature of the recording machine is necessary to interpret the electrical potential characteristics of ureteral peristalsis. For this reason, an explanation of the terminology of monopolar and bipolar leads (partially quoted from Barker[2]) is presented before the description of the nature of ureteral peristaltic action potentials. "... The two poles of all electric measuring instruments ... have been arbitrarily standardized and designated as positive and negative. The arrangement is such that, when the positive pole of a battery is connected to the positive pole of a voltmeter (or an EKG machine) and the negative to the negative respectively, the registration is to the positive side. If the battery connections are reversed, the

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[2] Barker, J. M.: The Unipolar Electrocardiogram. New York: Appleton Century-Crofts, 1952.

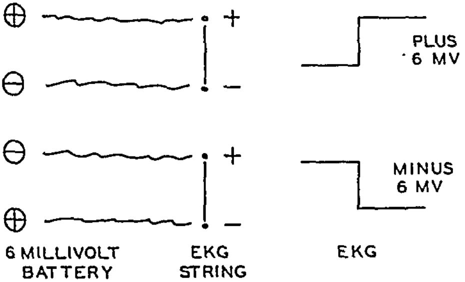

FIG. 3. Polarity of the EKG record in relation to positive and negative poles of a battery is shown on diagram (Barker[2]).

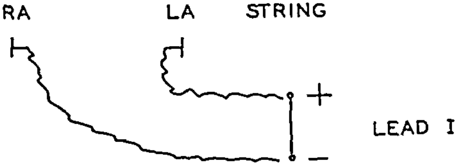

FIG. 4. Polarity of lead I of EKG machine is shown (Barker[2])

registration will be exactly opposite." This is depicted in figure 3 (from Barker). Also, ". . . any lead that measures the difference in potential between two points, one of which is positive and the other negative, or both of which are positive but one more positive than the other, or both of which are negative but one more negative than the other, is a bipolar lead."

The polarity of lead I of a standard EKG machine is shown in figure 4. This lead is the one routinely used in these experiments. The RA lead is connected to one intraluminal electrode and the LA lead to the other. Thus these recordings of ureteral peristalsis are bipolar in nature. A unipolar lead is defined as a lead in which one of the electrodes is placed outside the electrical field (theoretically at infinity), and by definition its electrical potential always is zero. Unipolar recordings of ureteral action potentials are taken by placing one electrode in the ureteral lumen, the other at some distant point. If we assume that the electrical potential of the latter electrode is zero, then the potential of the intraluminal electrode (minus zero) equals the potential difference recorded. Since the intraluminal electrodes of bipolar leads usually were 30–35 mm. apart in these experiments and the length of the electrical wave was less than this, little difference was seen between the recorded ureteral action potentials of a unipolar lead and those of the bipolar leads.

RESULTS

Nature of the action potential of human ureteral contraction. In figure 5 is seen the action potential of a human ureteral peristaltic wave obtained under optimum recording conditions. The recorded duration of these waves is 0.4 to 0.6 seconds

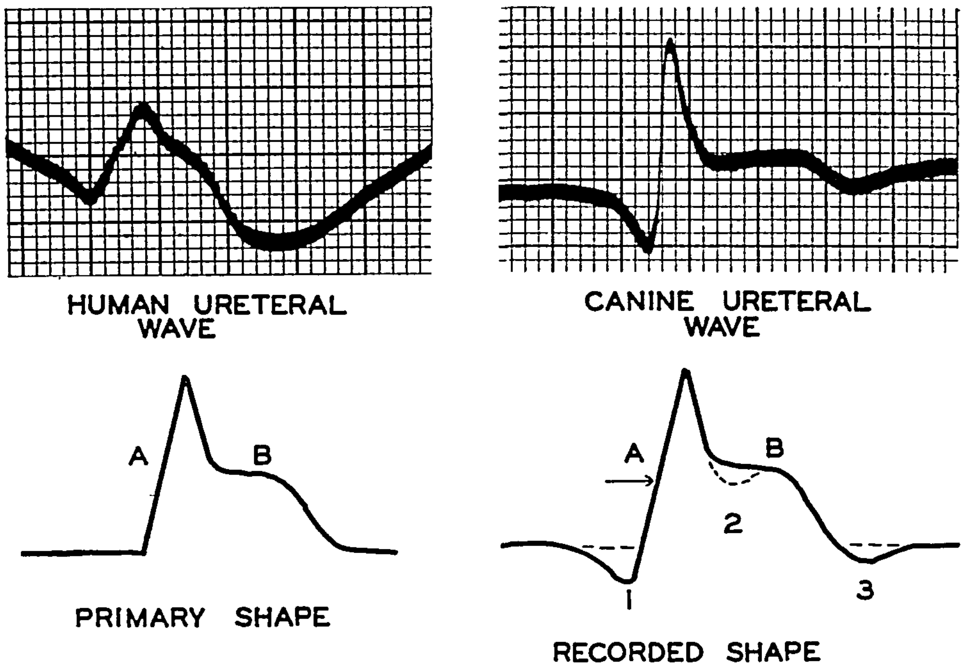

FIG. 5. Recorded electrical activity at negative intraureteral electrode is shown above. Human ureteral action potential is on left, that of dog on right. Below, on left, is diagram of what is believed to be primary shape of action potential, and on right, its recorded shape. Rapid major deflection, *A*, is followed by phase, *B*, which after its initial rapid portion has a slower phase or "shoulder". *1*, *2* and *3* are positive pulses seen in recorded wave. These small positive deflections are believed to be due to approach to electrode, *1* and recession from it, *2* and *3* of areas of electrical activity (negativity). (The deflection, *2* has been seen infrequently in recordings from human ureter.) Point which is used to measure peristaltic wave velocity is indicated by arrow along *A* in diagram of recorded wave.

and their maximum voltage about ½ mv. The action potentials of human ureters have lower average voltages than those of the canine ureter,[3] possibly because of a thicker mucous membrane lining of the ureter of the former. This factor may interfere with recording of the total wave duration in the human ureter, since low voltage action potentials will fail to show the total duration of the slow phase of recovery. Although it has been more difficult to record sharp high voltage action potentials from the intact human ureter than from the dog, sufficiently good recordings have been obtained in man to indicate the presence of a type of primary wave shape quite similar to that in the dog (fig. 5). Variations in voltage and duration of the action potentials recorded from a single ureter or from different ureters cannot be compared quantitatively one with the other. These variations may be and probably often are, secondary to changes in contact between the ureteral wall and the electrode caused by the passage of urine or by the contraction itself.

Voltage changes other than peristaltic action potentials seen in the standard bipolar recording. 1) Voltage changes caused by the passage of urine: The effect of the passage of a bolus of urine has been shown in the dog[3] to produce a slow

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[3] Butcher, H. R. and Sleator, W.: A study of the action potentials of ureteral peristaltic waves. To be published, Am. J. Physiol.

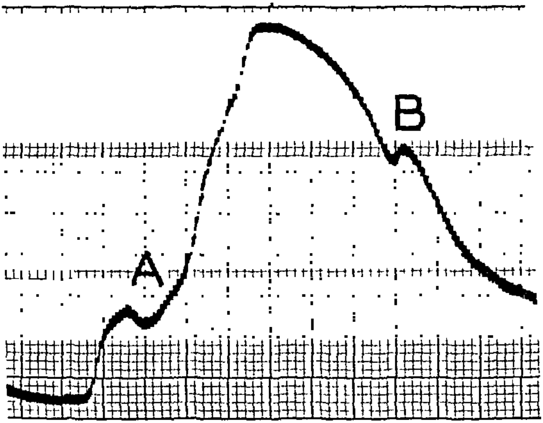

Fig. 6. *A* and *B* represent bipolar action potentials of peristaltic wave superimposed upon large, slow voltage change (or interelectrode resistance variation) caused by associated passage of urine.

voltage change of varying magnitude and sign. Records from human ureters show a similar voltage change associated with the peristalsis. This slow voltage change may appear before, after, or coincident with the action potential. An example of this slow voltage change is seen in figure 6. The magnitude of this voltage change varies, and at times is sufficiently great to require marked reduction in sensitivity of the machine in order to record it. For this reason, identifiable action potentials are not always recorded, although small notches indicating them usually are seen. A significant slow voltage change is not always seen with the passage of an action potential. This may mean one of two things: a) no urine is passing the electrodes—the wave may be caused by the presence of the catheter or b) the positive and negative resistance variations caused by the passage of a bolus of urine cancel each other. Variation in magnitude, rapidity, and sign of the slow voltage changes seen, indicate the latter may occur.

2) Voltage changes secondary to respiratory and cardiac function: During the period of recording in the patient who is awake, any significant movement by the patient will produce deflections of the recording arm. Respiration and cardiac activity at times are recorded. Respiratory motion may produce a quite regular type of slow voltage change of either sign during a specific period of recording (fig. 7, *A*). This voltage effect often varies in magnitude and, with a large inspiration, may be marked (fig. 7, *B*).

Diminutive cardiac EKG recordings are seen at times on the record taken from the two intraluminal electrodes. The magnitude of this electrocardiogram usually is quite small, but occasionally may be of sufficient size to interfere with interpretation of the electroureterogram (fig. 8). Relatively large electrocardiograms more often appear in the record when the intraluminal ureteral electrodes are far apart.

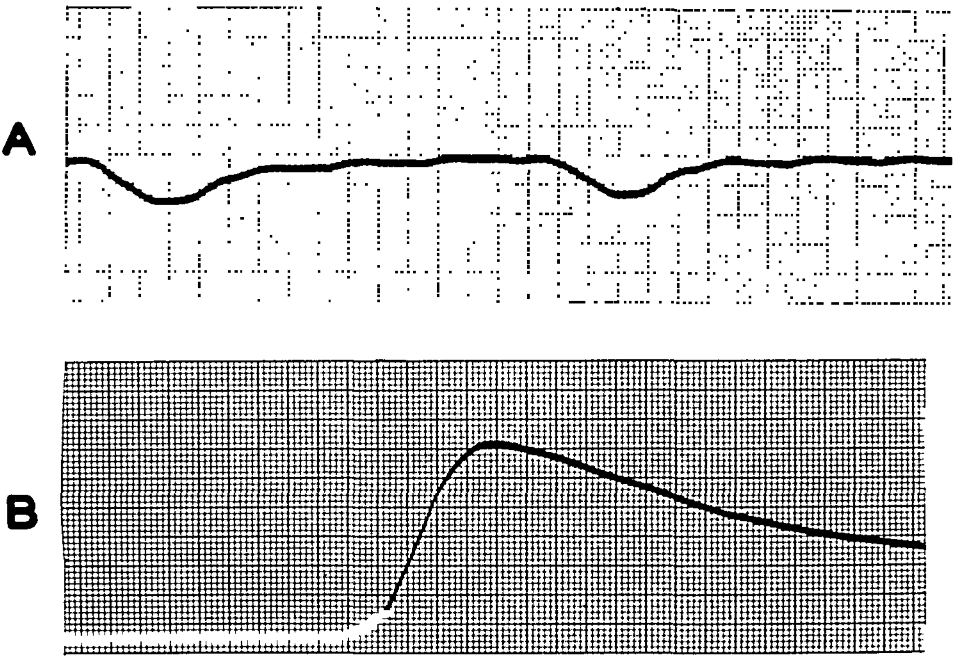

FIG. 7. Records of voltage changes caused by respiratory motion are shown. Above, *A*, is seen a voltage effect occurring every 3 seconds which was correlated with respiratory motion. Below, *B* is record resulting from single deep inspiration.

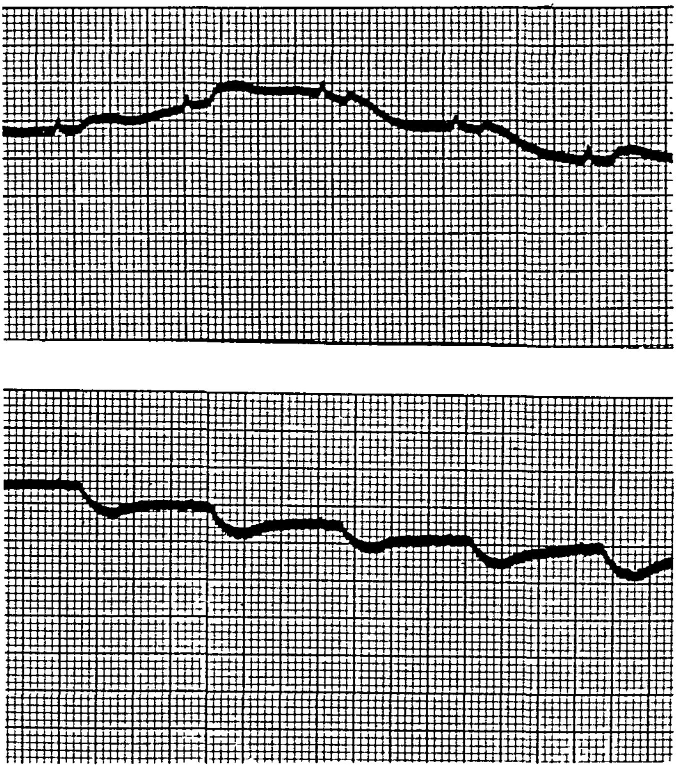

FIG. 8. Two examples are shown of rather marked cardiac activity which may be seen when recording from two intraureteral electrodes.

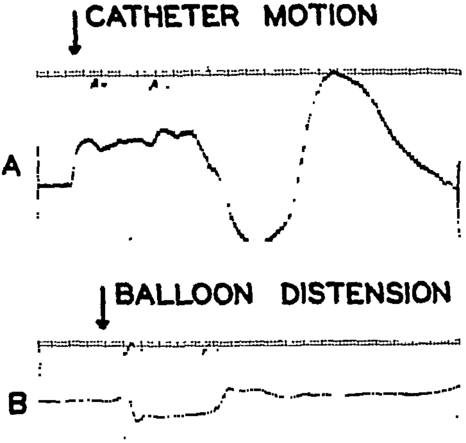

Fig. 9. *A*, stimulating effect of jiggling ureteral catheter is recorded. Large slow voltage effect following action potentials (A^+ A^-), probably was caused by passage of urine. *B*, distension of small, intraureteral balloon above recording electrodes stimulates propagating peristaltic action potentials (A^+ A^-).

Stimulation of peristaltic waves in the human ureter. In some of the patients studied cystoscopically, jiggling the ureteral electrode catheter produced propagating peristaltic action potentials (fig. 9, *A*). Study of the ureter during operation showed that distension of an intraureteral balloon stimulated peristalsis (fig. 9, *B*). Pinching of the ureter with smooth tipped forceps also consistently stimulated peristaltic waves in the patient studied immediately after nephrectomy. Also worthy of note was the absence of peristaltic action potentials in this patient during 10-minute periods of recording from the intraureteral electrodes carried out 24 and 48 hours after the nephrectomy. Stimulation by distension and local irritation of the human ureter did not appear to differ significantly from similar stimulation of the canine ureter.

Direction of peristaltic waves. The bipolar recording of the progress of the action potential of a peristaltic wave along the ureter reveals the direction of this wave since the polarity of each electrode is known. The great majority of peristaltic waves recorded in humans have propagated downward (fig. 10, upper record). However, upward coursing waves (fig. 10, lower record) occasionally are seen associated with the activity resulting from motion or insertion of the ureteral electrode catheter. The lower recording electrode may act as the source of stimulus in these instances.

Frequency of peristaltic waves. In the intact human ureter, the frequency of waves has varied from 0.8 to 10.0/min. (table 1). The occurrence of waves may be regular or grouped in two's or three's with a more prolonged interval between the groups of waves than between each wave. Occasionally, the pause between groups may last two to three minutes.

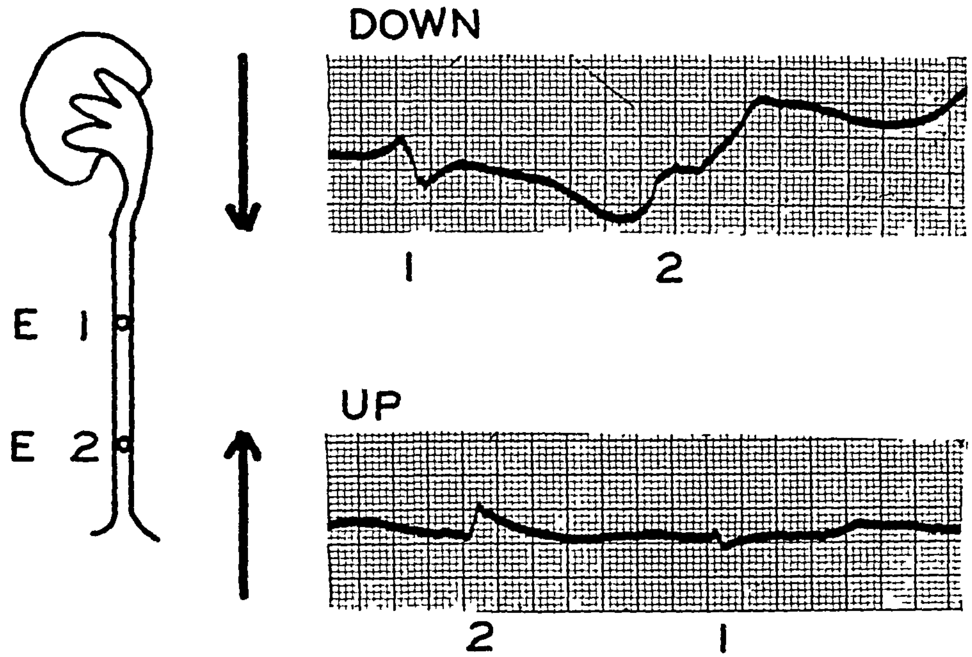

FIG. 10. Above is shown record of peristaltic wave propagating down ureter, while below is record of a wave coursing upward. Presence of peristaltic action potential at each electrode (E1 and E2) is indicated beneath each record.

TABLE 1. *Human ureteral peristaltic activity*

Patient	Frequency Waves/Min.	Velocity MM/Sec.
M. Br	4-8	21-31
M. Ba	4	25-35
P. H.	0.8-3	21-31
L. J.	5	37-41
N. C.	6	33-45
E. B.	3-10	33-40

The conduction velocity of peristaltic waves. The velocity of conduction of the action potentials along the ureter can be determined by this method of bipolar recording. Thus,

$$V = \frac{DE \times 25}{DS}$$

where V is velocity in mm/sec., DE the distance in millimeters between the recording electrodes, and DS the distance on the record between the recorded action potentials. In all instances, the speed of the recording paper has been 25 mm/sec. The velocity of ureteral peristaltic waves varies in a given patient about 10–15 mm/sec., and from patient to patient by as much as 20 mm/sec. (table 1). The velocity usually is between 25 and 35 mm/sec. but the extremes for the intact human ureters recorded to date have been 20 and 45 mm/sec.

As in the dog,[3] the velocity of peristaltic waves correlated with their frequency within the limits of variation of the velocity (fig. 11). The shape of the action

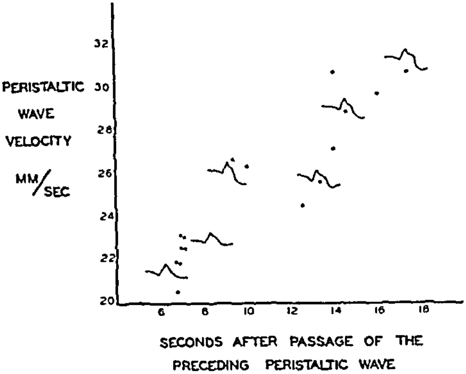

FIG. 11. Correlation of variations in wave velocity with time since passage of preceding peristaltic wave is shown. Change in shape of phase B of action potential associated with velocity variation is depicted by traced wave shapes reproduced upon graph near points representing velocity of each. Data graphed here were taken from record of patient studied during cystoscopic examination.

potentials also has been found to vary with the velocity of conduction (fig. 11). This phenomenon, first discovered from study of the canine ureter, is evident only in records where the action potentials are optimally recorded, since only in these is the slow phase of recovery (phase B) evident. As the velocity falls the "shoulder" of phase B of the action potential disappears. It returns as speed of conduction increases.

Peristaltic waves stimulated by balloon distension show a similar correlation between frequency and velocity as seen in spontaneously occurring peristalsis. In the patient studied immediately after nephrectomy, it was possible by varying the interval of balloon distension to define for this ureter an *absolute refractory period* and a *period of reduced wave velocity* (fig. 12, *A*). In this instance a peristaltic wave could not be stimulated less than 3.2 seconds after a preceding one, no matter how forceful the balloon distension. The duration of the period of reduced wave velocity was 5–6 seconds.

Repetitive distension stimulation produced a reduction in velocity of the resulting waves below that which one might predict from the time elapsed since the preceding wave (fig. 12, *B*). The cause of the period of reduced wave velocity and of the effect of repetitive stimulation upon it is as yet unknown. Following the manipulation of the upper end of this ureter incident to its study by balloon distension, stimulation of peristaltic waves by pinching in this region was no longer possible.

The effect of surgical mobilization upon the conduction of peristaltic waves. The effect of elevating the cut end of the ureter in preparation for anastomosis to an isolated segment of ileum was investigated by recording from two intraluminal electrodes placed within the mobilized segment of ureter and comparing the records with those obtained from two electrodes situated within the remaining

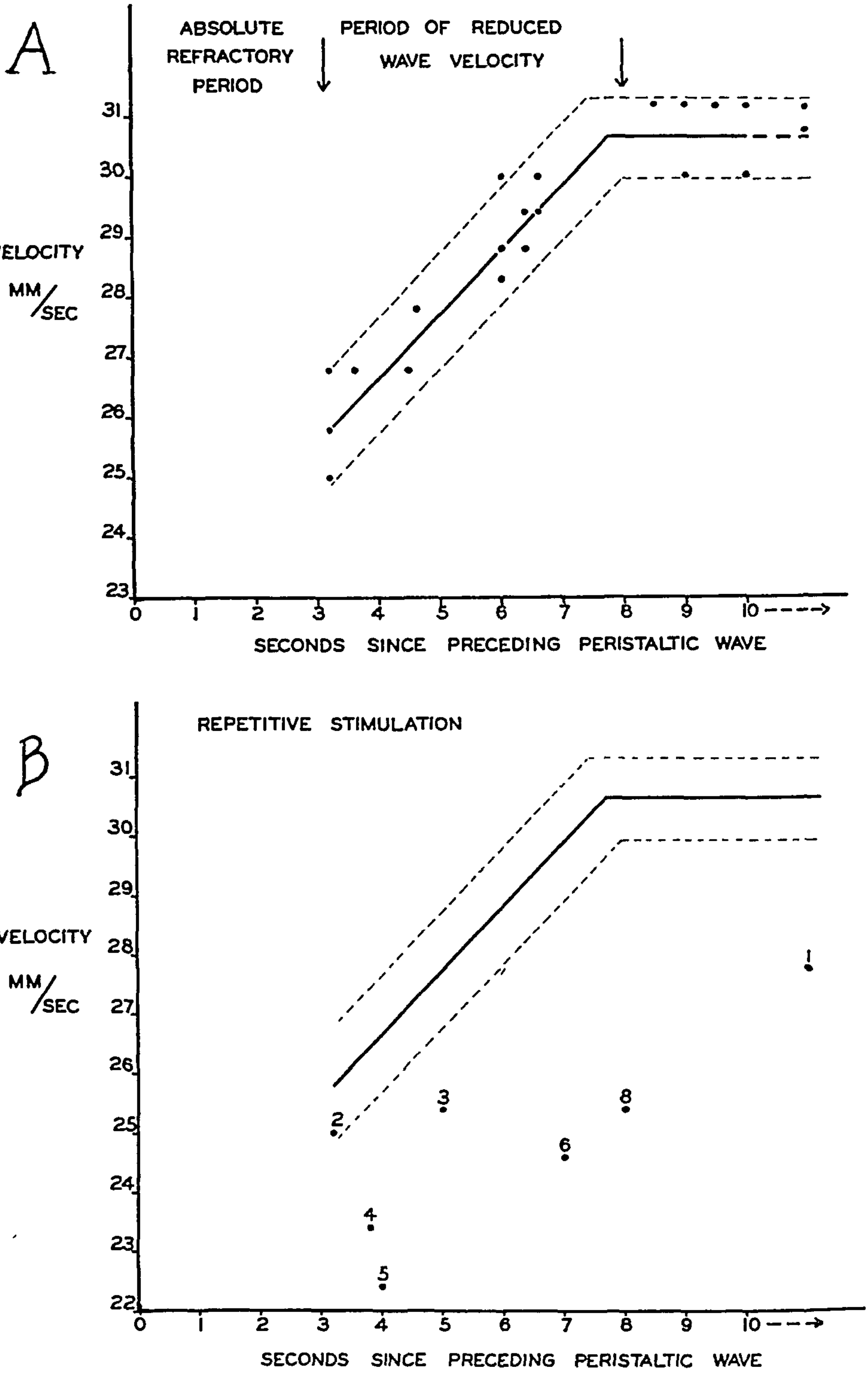

FIG. 12. *A*, graph shows relationship between velocities of stimulated peristaltic waves and time since passage of preceding wave. Stimulation was carried out immediately after nephrectomy by balloon distension and recordings taken from intraureteral electrodes placed preoperatively. Arrows above separate absolute refractory period from period of reduced wave velocity.

B, effect of repetitive stimulation upon velocity of resulting peristaltic waves in relation to period of reduced wave velocity is shown. Whereas superimposed graph from *A* 13 was obtained by comparison of velocities of peristaltic waves following one or two distensions of stimulating balloon, points graphed here represent wave velocities resulting from repeated balloon distension at 3–6 second intervals. Initial wave, *1* was stimulated 15 seconds after passage of last of three preceding stimulated waves. Seventh stimulus, 4 seconds after passage of the sixth wave, failed to stimulate peristaltic wave but 4 seconds later (8 seconds after passage of sixth wave) eighth stimulation resulted in propagating wave. Four seconds later, a ninth stimulus again failed to produce a propagating peristaltic action potential.

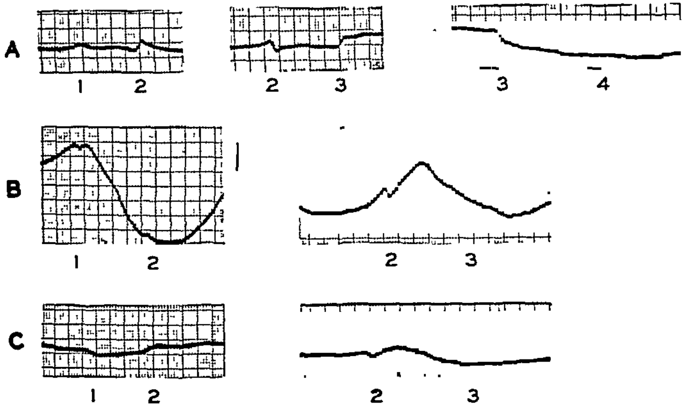

Fig. 13. All records shown were taken from intraluminal electrodes placed in right ureter prior to completion of ureteroileostomy. Electrodes *1* and *2* were placed in undisturbed upper ureter (electrode *1* nearest to kidney) while electrodes *3* and *4* were within mobilized portion immediately above ureteroileal anastomosis; electrode *4* was nearest anastomosis, electrode *3* near upper limit of mobilized ureteral segment. Records taken immediately upon completion of the operation, *A*, show failure of downward propagating action potential to record at electrode *4* although its presence at *3* is definite. In records taken 24 hours *B* and 48 hours *C* after operation action potentials record only at electrodes *1* and *2*.

unmobilized ureteral segment. Action potentials were recorded at the usual speeds and frequencies from the unmobilized ureter. However, in 4 patients studied, peristaltic action potentials did not appear in the mobilized segment of ureter during the 10-minute periods of recording performed daily during the first three postoperative days. (In two of these patients the recording contained sufficient voltage changes correlated with cardiac rhythm and respiratory activity to interfere with recognition of low voltage peristaltic action potentials possibly present.) In another patient, the electrode situated within but near the upper margin of the mobilized segment of ureter recorded action potentials after operation, but 24 hours later the action potentials were absent at this electrode and remained so (fig. 13). Although the action potentials in still another patient were poorly recorded, a return of conduction through the mobilized segment seemed to appear on the third postoperative day and persisted on the fourth.* However, the velocity of the wave through this segment was markedly reduced (13.4 mm/sec. compared to 25–30 mm/sec. in the unmobilized segment). On the third postoperative day some of the peristaltic waves recording at the proximal electrode in the mobilized segment did not propagate to the lowest electrode in this segment. By the fourth day, however, all waves entering the mobilized segment of ureter propagated at least as far as the lowest recording

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* This is the only patient so far studied in whom the ureteral electrode assembly was left in place for 4 days. Although no clinical evidence of urinary tract complications have been seen as a result of the inlying electrode assembly, such probably is more apt to occur the longer the assembly is left in place.

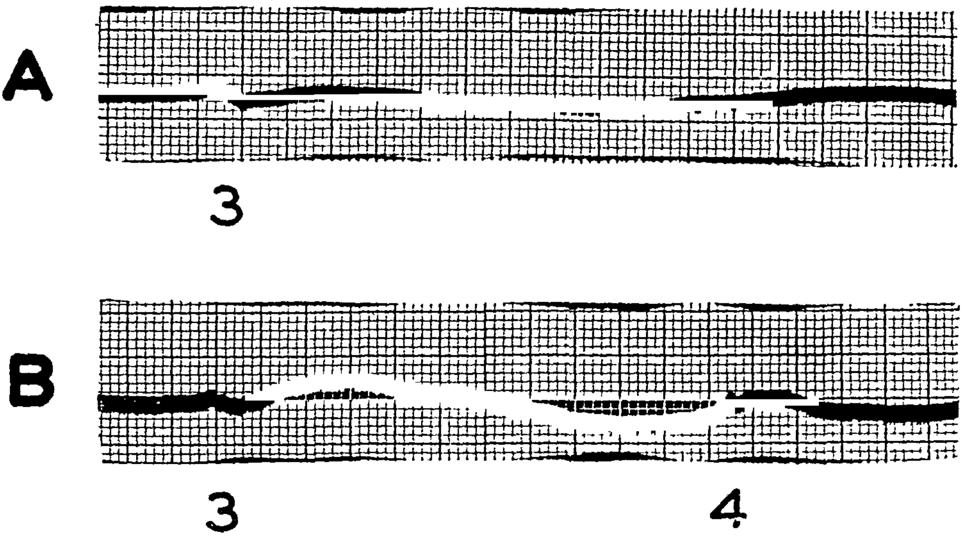

FIG. 14. Records from electrodes placed in mobilized segment of ureter were made 3, *A* and 4, *B* days postoperatively. Prior to these days, records failed to record any definite action potentials in mobilized segment. Some of waves recording at electrode, *3* on third postoperative day failed to reach electrode, *4* nearest ureteroileal anastomosis, *A*. All waves recorded on fourth postoperative day involving electrode, *3* also recorded at electrode *4*. Velocity of these propagating waves between electrodes *3* and *4* was reduced.

electrode (fig. 14). Recordings from the electrodes in the mobilized segment of ureter were not simultaneous with recordings from the undisturbed ureter except when performed between one of the upper pair and one of the lower pair of electrodes (fig. 13) since only a single channel recorder was used. Recording from the electrodes in the mobilized segment of ureter was for at least 10 minutes. It would appear unlikely that spontaneous peristaltic activity would suddenly cease for such a period, just after 4–6 peristaltic waves per minute have been recorded in the unmobilized segment of the ureter.

DISCUSSION

Engelmann[4, 5] described many of the physiological characteristics of the ureteral activity using a method of careful visual observation and anatomic study of the ureters of animals. He concluded that the ureteral peristalsis is myogenic in origin and that neural stimuli are not initiating factors. Subsequent investigators (referred to by Gruber[6]) all of whom did not agree with his conclusions, used various methods of study including direct visual observations, the recording of pressure changes, and analysis of the nature and volume of the flow of urine. Anatomic and pharmacologic methods also were used. The hydrophorograph was described in 1924 for the study of ureteral activity in man.[7] Further development

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[4] Engelmann, T. W.: Zur Physiologie des Ureter. Pfluger's Arch. f. d. ges Physiol., **2:** 243–293, 1869.

[5] Engelmann, T. W.: Beitrage zur allegemeinen Muskel-und-nerven physiologie. Pfluger's Arch. f. d. ges. Physiol., **3:** 248–326, 1870.

[6] Gruber, C. M.: The autonomic innervation of the genito-urinary system. Physiol. Rev., **13:** 497–609, 1933.

[7] Trattner, H. R.: A method of recording contractions of the intact human ureter. J. Urol., **11:** 477–487, 1924.

of this pressure-flow method followed and the results of extensive studies of the human ureter by this method have since been published[8-11]

Investigation of the action potentials of isolated ureteral smooth muscle has been carried out by Bozler[12-15] Orbeli and Brucke[16] and Mingers[17] have studied the action potentials of the canine ureter in situ Orbeli and Brucke used a string galvanometer and nonpolarizable electrodes placed about the mobilized lower ureter They obtained bipolar records of the action potentials of peristaltic waves and consequently were able in part to determine the speed of the peristaltic waves down the ureter The method employed by Orbeli and Brucke could not readily be applied to the study of the ureter in man However, Mingers employed intra-ureteral electrodes which could be used to study the electrical activity in human ureters

In order to attack the unsolved problems of ureteral function, it seemed desirable to simultaneously record both action potentials and mechanical contractions of the ureter This correlation has been carried out for the canine ureter and reported elsewhere[3] The electrical method of study records the smooth muscle action potentials of the ureter and has proved a satisfactory method of investigation of the intact ureters of animals and man

The application of the electrical method of study to the investigation of human ureteral activity has shown that the frequency, direction and velocity of peristaltic waves can be determined Intraluminal electrode recording is a satisfactory one when there is no marked discrepancy between the size of the ureteral lumen and the electrode Indeed, it would appear from studies of the canine ureter that the intraluminal position of the electrode is superior to the intramuscular position obtained when a needle type electrode is used

The characteristics of the human ureteral action potentials obtained under optimal conditions are as follows (fig 5) There is one major deflection (A) which is usually preceded by a small one of opposite sign (1) The return toward neutrality (B) following this major deflection is initially rapid but then is characterized by a slow phase or "shoulder" At the beginning of this slow phase or "shoulder", one occasionally sees in human ureteral action potentials a small deflection (2) which represents relative positivity at the electrode probably

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[8] Trattner, H R Graphic registration of the function of the human ureter with the hydrophorograph J Urol , **28**· 1–33, 1932

[9] Lapides, J The physiology of the intact human ureter J Urol , **59** 501–533, 1948

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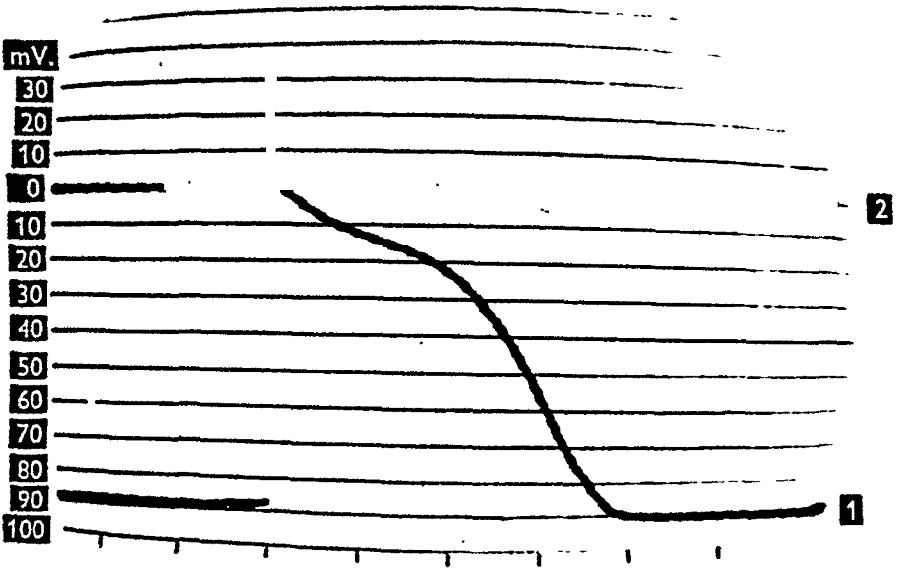

FIG. 15. Monopolar canine cardiac action potential recorded from an intracellular electrode is shown. (Figure reproduced from Draper and Weidmann.[18])

caused by the recession from it of the peak phase of the area of electrical activity (negativity). A small deflection (3), again of opposite sign, may follow the return toward neutrality. Deflections (1) (3) probably also represent the approach and recession respectively of the area of activity (negativity) to and from the recording electrode. The major deflection A generally is interpreted as being due to depolarization of the contracting muscle cells, while phase B is considered representative of electrical repolarization. The characteristics of ureteral peristaltic action potentials are similar to those of other active conducting tissue. Their comparison with a canine cardiac action potential (fig. 15) reproduced from Draper and Weidmann[18] exemplifies this similarity.

With bipolar intraureteral electrodes 25–35 mm. apart, the electrical record consists of two parts, one being the mirror image of the other. The ureterogram illustrated in figure 9, *B* is characteristic of human ureteral activity when slow voltage changes due to the passage of urine are absent. The effect of voltage changes incident to the passage of urine upon the recording of the action potentials is shown in figure 6. Here the action potentials appear as notches superimposed upon a massive slow voltage change which may be of either sign. The position of the action potentials are not constant in relation to this slow voltage change; they may precede, be superimposed upon, or follow it. It is assumed that these slow voltage changes are due to alterations in the resistance of the interelectrode portion of the circuit caused by urine passing through the ureter.

There are definite variations in the frequency of peristaltic waves in the intact human ureter (0 8–10 0 min) (table 1) The factors which influence frequency remain to be investigated

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[18] Draper, M. H. and Weidmann, S.: Cardiac resting and action potentials recorded with an intracellular electrode. J. Physiol. **115:** 74–94, 1951.

The velocity of conduction of an action potential along a human ureter varies (20–45 mm/sec) Two factors have been shown to be correlated with velocity (fig 12), namely, 1) the period of time elapsing between peristaltic waves and 2) the shape of phase B of the peristaltic action potential The significance of the latter and its relation to peristaltic conduction are yet unknown Further investigation into the relationship of velocity of conduction and the shape of phase B is being conducted in the dog The velocity frequency correlation also has been found present in the canine ureter, where by means of balloon distension stimulation of peristaltic waves, an absolute refractory period and a period of reduced wave velocity have been defined These periods have been defined (also by balloon distension stimulation) in one grossly normal human ureter (fig 13) studied immediately after nephrectomy for nephrolithiasis In this instance, both periods were of longer duration than usually found in the canine ureter [3]

That the origin of human ureteral peristaltic waves is not entirely autonomous is indicated by the fact that no spontaneous peristaltic waves were recorded from the ureter after nephrectomy during 10 minute periods of recording 24 and 48 hours after operation

It would appear that conduction of ureteral peristalsis in the human being is, at least temporarily, interfered with by cutting the ureter, mobilizing two to three inches of it, and anastomosing it to a small intestinal segment The records shown in figure 14 indicate that the effect on conduction may not be immediate in the area where the mobilized meets the unmobilized segment of ureter, but may appear later, that is, within the next 24 hours The capacity to conduct peristaltic waves is ultimately regained by the mobilized segment (fig 13), but for a time after the capacity to conduct is regained the velocity with which the peristaltic waves course over the mobilized segment is lower than normal How long the conductional rate decrement lasts is not yet known

Studies in both dog and man have shown temporary interference with the conduction of ureteral peristaltic waves after the trauma of surgical mobilization Whether this is an important causal factor in the production of transitory hydronephrosis seen after ureteral transplantation is unknown

SUMMARY

The electrical recording of the action potentials in human ureteral peristalsis is feasible from intraluminally placed ureteral electrodes

The recorded action potentials of human ureteral peristalsis are similar to those that have been recorded in the canine ureter [3]

A large, slow voltage change in the recording is often associated with the peristaltic action potentials This is presumed to be due to changes in the circuit caused by the passage of urine

Voltage changes due to motion and respiratory or cardiac activity may interfere with optimum recording of peristaltic action potentials

Frequency of peristaltic waves in the intact human ureter vary (0.8 to 10.0/min.).

Velocity of conduction of peristalsis is measurable by the electrical method of study. It is shown to vary conversely as the interval since the passage of the preceding peristaltic wave (fig. 11). Velocity also shows correlation with the shape of the action potential (fig. 11).

An absolute refractory period and a period of reduced wave velocity have been defined by balloon distension stimulation.

The surgery upon the ureter necessary to establish ureteroileal anastomosis in patients requiring ileal bladder substitution interferes, at least temporarily, with peristaltic wave conduction through the mobilized segment of ureter.

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POLYETHYLENE AS PARTIAL URETERAL PROSTHESIS IN DOGS

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The recent advent of nonreactive plastics has greatly aided certain types of repair and replacement surgery Polyethylene, the least reactive of those generally available, has been used in gynecological,[1] cardiovascular[2] and neurological surgery[3] and in urology[4]

The possibility of using this material as replacement for a part of the ureter was investigated by Heidmann[5] in rabbits He found that small tubes became obstructed with precipitates, and that hydronephrosis developed and the animals died in uremia We considered his use of the rabbit unfortunate because of the small tubing required and because of the very great tendency for the urine of herbivores to form precipitate For this reason, a study was initiated in dogs After the beginning of our experiments, Tulloch[6] published an account of the successful use of this plastic for bilateral ureteral replacement in a human Our report is considered to corroborate his and to show the condition of the prosthesis in the surviving animal

METHODS

In the first animal studied, the left ureter was exposed retroperitoneally, and a segment 3 inches long was removed and replaced with polyethylene tubing (2 mm) This animal was subjected to excretory and retrograde pyelography, neither of which gave any unequivocal indication of the state of the left kidney However, there was no sign of renal hypertrophy on the x-ray, nor were there any other signs of malfunction while the animal was kept in the animal quarters for over a year Unfortunately, this animal was used in a terminal experiment and cremated before autopsy

Since it seemed that this animal had shown the possibility of partial ureteral replacement, a series of three animals was subjected to bilateral partial ureteral replacement The segments replaced varied from 1½ to 4 inches One animal was sacrificed after 6 symptom-free weeks, the ureters were removed, examined macroscopically, and then sectioned and stained with hematoxylin and eosin The two other animals have shown no deficit in renal/ureteral function and are

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Aided by a grant from the State of Washington Research Fund for Biology and Medicine
Accepted for publication September 22 1954

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[5] Heidmann, J P Polyethylene tubing in experimental surgery of ureter Brit J Surg **37** 105–106 1949

[6] Tulloch, W S Restoration of the continuity of the ureter by means of polythene tubing Brit J Urol **24** *42–45, 1952*

surviving after 13 months. One of these animals delivered a litter of seven 4 months after implantation. In order to terminate a second pregnancy, a hysterectomy was performed 6 months after the implantation and at this time a gross examination of the implants was made.

RESULTS

No comment will be made about the first animal studied. The second group of three animals showed no impairment of renal function. The two surviving ani-

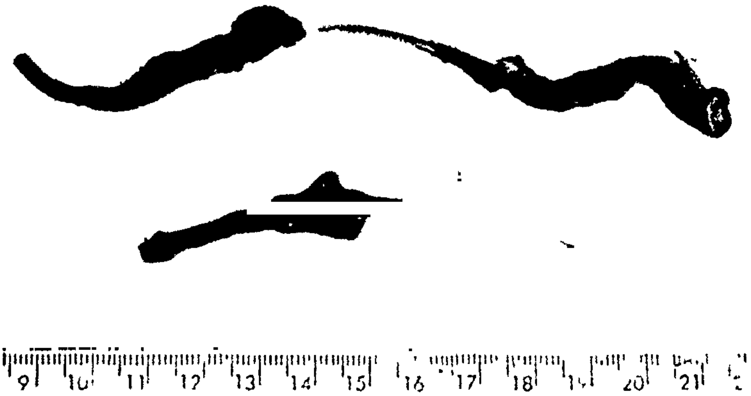

FIG. 1. Two segments of ureter from dog sacrificed 6 weeks after polyethylene implantation. In upper segment connective tissue has started to connect two stumps. In lower section there is a complete connective tissue bridge.

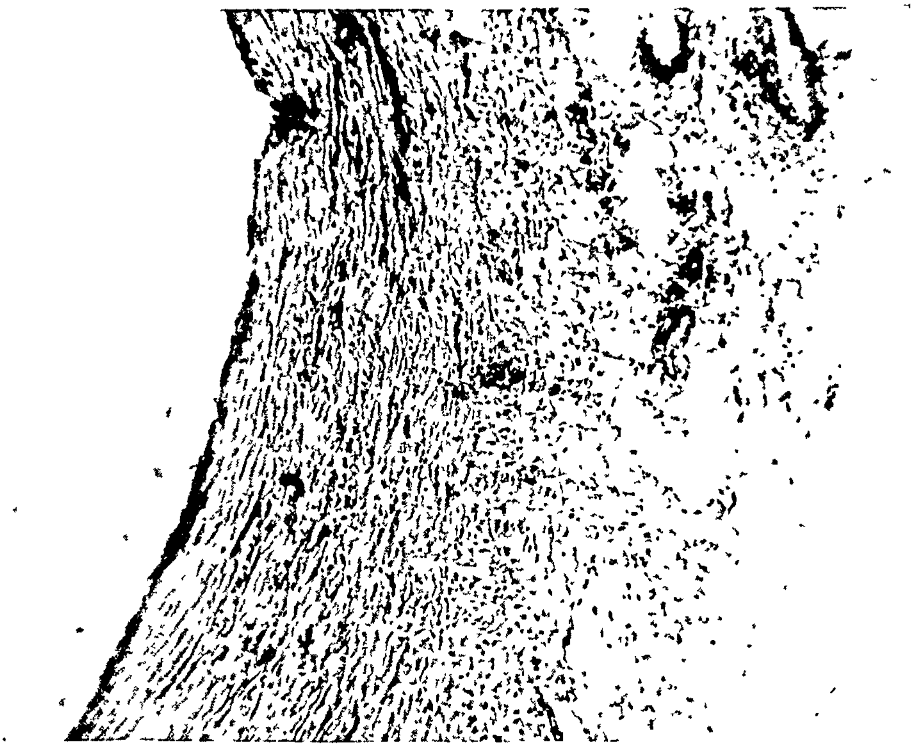

FIG. 2. Section from lower specimen of figure 1. Note closely packed, connective tissue cells around polyethylene tube, showing few signs of inflammation.

mals are in excellent condition One has been adopted by one of the writers' colleagues

The ureters of the sacrificed animal are shown grossly in figure 1 There is some increase in the size of the right ureter near the pelvis, but there is no precipitate within the lumen Tissue had grown over the plastic in the left ureter This tissue was adherent to the plastic but could be moved around the plastic Near the ligatures on the left ureter there were small nodules which contained accumulations of fluid The fluid was clear, had a pH of 7 0 and was without sediment It was not urine, and was considered the result of a foreign body reaction around the ligatures

The photomicrograph (fig 2) shows that the polyethylene tube replacing the right ureter became surrounded with connective tissue This tissue consists of small, densely packed cells immediately adjacent to the plastic with larger, looser cells at the periphery of the cellular tube There is little sign of inflammatory reaction within this tissue

Examination of the ureters in one of the two surviving animals at the end of 9 months showed the plastic to be completely encased in a connective tissue tube about 1 mm thick There were no nodules or other irregularities apparent in this sheath The kidneys were both producing urine although one appeared slightly larger than the other There was no hydronephrosis

DISCUSSION

These experiments have shown the feasibility of replacing part of the canine ureter with polyethylene The plastic, despite its nonreactive properties, may become encased in a healthy sheath of connective tissue It serves admirably as a conduit for the urine and in the dog, unlike the rabbit, does not accumulate precipitated matter from the urine Even in a 4-inch segment, the lack of ureteral motility does not cause an accumulation of casts The plastic ureters were not taken into the bladder Since dogs will not suffer retrograde infection as easily as humans, it is felt that any conclusions about replacing the entire ureter would not apply to the human

SUMMARY

Polyethylene partial ureteral prostheses have been installed in 4 dogs, unilaterally in one and bilaterally in three others Although definite results are not available, the first dog appears to have had normal ureteral function for 15 months In two of the latter three there have been no signs of deficit in ureteral function for 13 months The third dog was sacrificed 6 weeks after operation The ureters were found to be patent, the ureteral stumps were attached to the plastic by healthy connective tissue which on one side had completely enclosed the plastic Examination of one of the surviving 2 animals 9 months after operation showed both ureters to be enclosed in healthy connective tissue These results corroborate Tullock's finding that this plastic will serve as an excellent replacement for the human ureter

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URETEROPERITONEAL FISTULA: CASE REPORT OF A LATE BULLET WOUND COMPLICATION

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A rare and interesting late complication of a ureteral injury by a bullet is here presented.

Herman et al.[1], in a study of ureteral injury, reported on a case of a 19 year old male who suffered fatal peritonitis following ureteral trauma by a stone dislodger. Five days after ureteral instrumentation, much purulent fluid was found on surgical opening of the peritoneal cavity. It may be speculated that here also was a case of ureteroperitoneal communication.

Robinson et al.[2] reported on 25 war ureteral injuries, 18 of which were recognized only when a urinary fistula developed, from 2 to 10 days after primary surgery.. The ureteral injury was most likely overlooked due to the gravity and extent of the associated injuries. In complete division of the ureter, the only hope has been primary repair. As a late procedure, nephrectomy will have to be done, according to Everidge and Barnes.[3] Many excellent papers on war ureteral injuries have been published, but it is not within the scope of this paper to review the literature.[4]

CASE REPORT

J. T. H., Reg. No. 71420, 28 year old Negro, was admitted to the Lake City Veterans Hospital on February 11, 1953 complaining of marked abdominal distention. This had developed rapidly during the preceding 3 days. A few days previously, he had noticed vague discomfort in the left lower quadrant of the abdomen, accompanied by a few spells of nausea and vomiting. The patient gave a history of an abdominal bullet wound on December 20, 1952, fifty-three days prior to admission. There was no history of hematuria or urinary fistula after being shot. He was hospitalized at a private hospital and an operation performed, during which the patient stated that "parts of his intestines were removed." He was discharged from that private hospital on January 1, 1953 as completely healed.

On admission the patient was in considerable discomfort because of abdominal distention. Temperature was 100F, pulse 120, and blood pressure 110/60. Respiratory excursions were very limited. The abdomen was distended, tense and flat on percussion. Peristaltic sounds were not audible and a fluid wave was demonstrable. A small, oval scar, about 0.5 cm. in diameter, was present in the right upper quadrant and a long rectus incisional scar in the left abdomen. On rectal palpation the cul-de-sac was full and bulging. The prostate gland was normal. There was no edema of the lower extremities.

Accepted for publication November 3, 1954.

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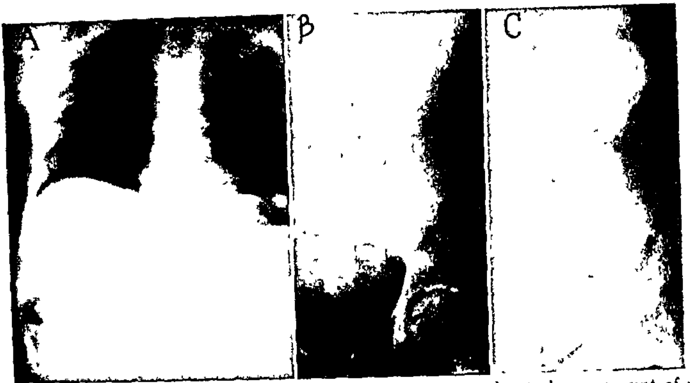

FIG. 1. *A*, x-ray of chest demonstrates elevated diaphragm due to large amount of abdominal fluid. *B*, x-ray of kidneys, ureters and bladder shows abdominal fluid and bullet shadow over left sacroiliac joint. *C*, left pyeloureterogram demonstrates extrarenal and intraperitoneal extravasation of contrast medium. Left ureteral catheter here shown was passed after injection of dye.

A chest x-ray (fig. 1, *A*) showed an elevated diaphragm. An x-ray of the kidneys, ureters and bladders (fig. 1, *B*) revealed fluid in the abdomen, and a bullet shadow overlying the uppermost aspect of the left sacroiliac joint. There were no dilated loops of bowel.

Blood count revealed hemoglobin of 11.8 gm., hematocrit 37, erythrocytes 3.8 million, and 15,500 leukocytes with 72 per cent granulocytes. Urinalysis showed 1 plus albumin and 3 plus pus, with a specific gravity of 1.008. Blood test for syphilis was negative.

The evening of admission, a paracentesis was done, and 5,700 ml. of a slightly hemorrhagic fluid removed. There was no abdominal tenderness on palpation after the paracentesis. The patient was given 500 ml. of blood on the evening of admission, and another 500 ml., the next morning. During that period, the patient was given 3,000 ml. of intravenous fluids, and also parenteral penicillin. Excretory urography revealed very little, if any, function of the right kidney. On the left there was hydronephrosis, caliectasis, and ureterectasis of the upper third of the ureter. The left ureter just above and below the shadow of the bullet was not visualized.

A cystoscopic examination was done, and pyeloureterograms made using a terminal eye occlusion ureteral catheter. The right pyeloureterogram was normal. On the left, four progressive pyeloureterograms (fig. 1, *C*) were taken, each one after the injection of 10–15 ml. of contrast medium. These films revealed progressive extravasation from the left ureter at the plane of the bullet, and extensive pooling in the peritoneal cavity. Indigo carmine, 5 ml., was next instilled, and then a paracentesis performed. Approximately 5000 ml. of a lightly blue-tinted and slightly hemorrhagic fluid was removed from the peritoneal cavity.

An operation was started. A left flank incision was made, and a marked degree of left retroperitoneal inflammatory induration, edema, and fibrosis found. The left ureter was identified with difficulty as it was buried in this mass of inflammatory tissue. The ureter was mobilized and traced with difficulty down to approximately the level of the brim of the pelvis. At this point, the ureter seemed to fan out and merge with the peritoneum. The ureter thinned out completely and further dissection at this point opened into the peritoneum. Palpation failed to locate the bullet, due to the marked inflammatory reaction, and continued search for it was not feasible. The length of the ureter available for reimplantation into the bladder was far too short. There existed also the mechanical barrier of the extensive retroperitoneal inflammation which prevented bladder, colonic, or ureteroureteral implantation. Accordingly, a nephrectomy was performed, since the right retrograde pyeloureterogram was normal, the patient was in excellent condition and a secondary nephrectomy was thereby eliminated. During surgery, patient received 1000 ml. of whole blood, and also intravenous fluids. Postoperative condition was good.

Pathologist's report (accession No. 5330): Grossly, the kidney measured 12 by 9 by 4 cm., to which was attached a section of ureter 8 cm. long. A cyst, lined by old clotted blood, measuring 2 cm. in diameter was present at the upper pole. On coronal section, the cortex measured 0.8 cm. at the end of the pyramid and 2.5 cm. overall at its thickest portion.

Microscopically (fig. 2), the glomeruli were intact and the tufts were rather small with large empty Bowman's spaces (estimated 3 to 4 times normal). The tubules were similarly dilated with a granular and/or vacuolated epithelial lining. Scattered through the section were microcystic spaces lined by flattened cells, and in some of these, a part of the lining consisted of more columnar cells; thereby showing that these were dilated Bowman's spaces in which the section

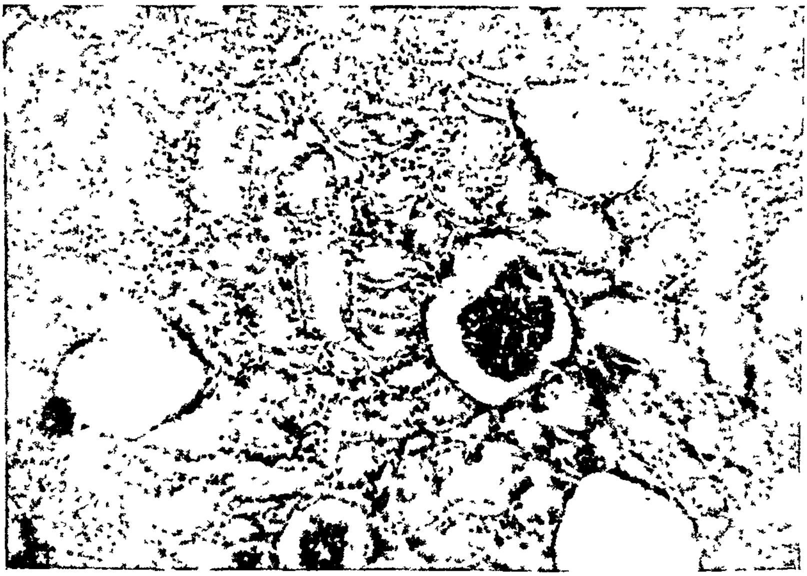

FIG. 2. Microscopic examination of kidney tissue mainly shows dilated Bowman's spaces and tubules.

had missed the glomerular tuft. There was surprisingly little inflammatory reaction and no vascular changes in the kidney.

Postoperatively, the patient was given streptomycin, penicillin, and intravenous fluids. A Cantor tube was passed on the first postoperative day and removed on the fourth, when the patient had a normal bowel movement, was passing flatus, and had normal peristaltic sounds. He became afebrile on the fourth postoperative day and intravenous fluids were discontinued. The remainder of the postoperative convalescence was smooth, except for prolonged wound drainage.

On the first postoperative day, the nonprotein nitrogen was 53 mg. per cent, blood chlorides 526 mg., icterus index 12, and CO_2 volume per cent 65. On the fourth postoperative day, the nonprotein nitrogen was 49 mg. per cent, CO_2 volume per cent 61, potassium 4.9 m/Eq., hemoglobin 12.6 gm., and hematocrit 35. By the thirteenth postoperative day, the nonprotein nitrogen had fallen to 27 mg. per cent. The hematocrit was 39, hemoglobin 13.6 gm., and sedimentation rate 28. A hanging-drop blood test for sickling was negative. An x-ray of the chest was now negative. A gastro-intestinal series was essentially negative except for colonic hypermotility and displacement of the terminal loops of small intestine.

The incision had been considered to have healed, but 15 days postoperatively, a serosanguineous discharge started from the midportion of the wound and continued for 6 weeks. This was treated with wound irrigations, and replacement of the Penrose drain. The patient was given terramycin and gantrisin orally, and penicillin and streptomycin parenterally. These preparations were prescribed for varying periods, and in various combinations. The drainage from the incision finally subsided, and the wound healed by May 1, 1953, when the patient was discharged from the hospital as cured.

On March 9, 1953, a letter was received from the private hospital, describing the extent of the injuries caused by the bullet wound of December 21, 1952. The liver edge had been lacerated. In addition to this, the following injuries were found: perforation of both walls of the stomach, perforation of the transverse mesocolon, two perforations of the mesentery of the ileum with tearing of the large vessels, perforation of the left posterior peritoneum with severing of the left colic artery. Approximately a liter of blood and considerable air were found in the peritoneal cavity. Immediate surgery had been done, which included resection of 30 inches of ileum, ligation of various severed vessels, closure of the two perforations of the stomach, and resection of a small portion of the liver. The rent in the left posterior peritoneum was enlarged to enable the surgeon to examine the ureter, which he stated was intact. However, he remarked that the severed ends of the left colic artery were ligated.

DISCUSSION

The pathogenesis of the ureteroperitoneal fistula can only be speculated upon, and one likely explanation may be that a surgical error was committed at the time of the primary operation. It may have been that what was ligated as severed left colic artery was actually the ureter. Then, some 53 days later, after absorption of the catgut ligature, urinary pressure may have resulted in re-establishing the patency of the proximal end of the left ureter. Since this lay beneath a previous peritoneal opening, and this was the avenue of least resistance, the urine created a ureteroperitoneal fistula.

In delayed surgery for ureteral injury, nephrectomy is frequently necessary, as was done in the case here presented. The short proximal ureter (8 cm.), combined with the factor of extensive retroperitoneal inflammation, made colonic, vesical, or ureteroureteral implantation impossible.

Since the preoperative excretory urogram showed an apparent lack of concentration of the contrast medium in the right renal pelvis, a left nephrostomy or ureterostomy, followed later by a secondary nephrectomy, would ordinarily be the recommended procedure. After deliberation at the operating table, the author decided upon a left nephrectomy because the right retrograde pyeloureterogram was normal, and the apparent poor function was therefore believed to be only temporary, probably of a reflex nature.

CONCLUSION

An unusual complication of a ureteral injury in the form of a delayed ureteroperitoneal fistula is here reported.

The diagnosis was made preoperatively, and this may be the second recorded case of this form of late complication of ureteral injury.

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THE REPAIR OF URETEROVESICOVAGINORECTAL FISTULA FOLLOWING IRRADIATION FOR CERVICAL CARCINOMA USING A FLAP OF BLADDER MUSCLE

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A H (M G H No 485703) A 50 year-old, nulliparous housewife entered the Massachusetts General Hospital on July 26, 1945 for treatment of a vesicovaginal fistula In 1937, at another hospital, a supravaginal hysterectomy had been performed for a leiomyoma In 1941 vaginal bleeding was noted and a cervical biopsy revealed "very early, well differentiated adenocarcinoma" Three courses of radium treatment and a single course of x-ray treatment were given This was followed a year later by intestinal obstruction, necessitating a double loop sigmoid colostomy Three months after this a vesicovaginal and vesicorectal fistula developed and persisted

Physical examination when she entered the hospital revealed a vagina approximately 8 cm in length with absence of the cervix and no evidence of recurrence of carcinoma At the apex of the vagina was an opening which communicated with the bladder Cystoscopic examination showed a vesicovaginal fistula 1 cm in diameter just medial to the left ureteral orifice Medial to this opening was a 2 mm opening which communicated with the rectum Excretory urograms revealed normal function of both kidneys

On August 1, 1945 the vesicovaginal and vesicorectal fistulas were excised transvesically The ureter was left in place and the openings closed with catgut sutures Seven days later it was evident that the repair had failed

In June 1949 the patient was readmitted for further evaluation She had had several attacks of left pyelonephritis An excretory urogram revealed that this kidney was moderately hydronephrotic The right kidney appeared normal On pelvic examination it was found that at the apex of the vagina was a 1 5 cm opening which connected with the bladder and the rectum There was no evidence of recurrent disease Cystoscopy was performed and in the region of the expected position of the left ureteral orifice was a 1 5 cm opening which connected with the apex of the vagina and the rectum The left ureter entered the fistulous tract as is shown in figure 1 It was demonstrated by x-rays and proctoscopic examination that the opening of the fistula in the bowel was approximately 12 cm above the anus and that there was complete obliteration of the sigmoid just below the colostomy The patient agreed to have another attempt made to repair the fistula with the provision that the length of the vagina be maintained

Under endotracheal gas oxygen ether anesthesia, through a suprapubic midline incision, the dome of the bladder was exposed Dense scar tissue made freeing of the left side of the bladder difficult, therefore, a left lower quadrant incision was also made This joined the lower end of the midline incision, as illustrated on the diagram (fig 2) The retroperitoneal space was easily entered, the ureter

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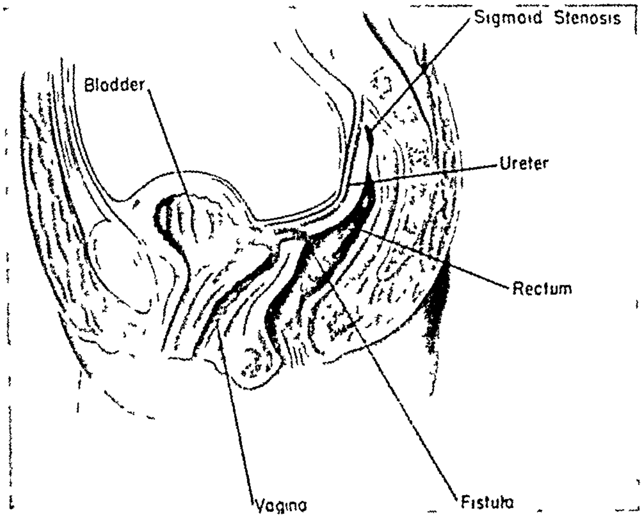

FIG. 1. Sagittal section showing fistulous tract joining bladder, vagina, ureter and rectum.

was identified and followed down to the fistula. A midline opening approximately 9 cm. in length was made in the dome of the bladder (fig. 3, *B* and *C*) and the left side of the bladder was completely freed. The ureter was divided close to the fistula. The fistula between the bladder, vagina and rectum was excised. The opening in the rectum was closed in two layers, using No. 00 chromic catgut. The end of the vagina was closed with a similar running suture. The site of the fistulous opening in the bladder (fig. 3, *A*) was joined to the lower portion of the midline bladder incision (fig. 3, *B*) in order to facilitate closure of the opening. The closed openings in the rectum and the vagina and the proposed closure of the opening in the bladder were very close together. It was decided to separate these closures by swinging a viable muscle flap in the hope that if the suture lines broke down the viable muscle would help them heal. The possibility of using some of the psoas muscle was considered. It became apparent that using a flap of bladder muscle probably would be much simpler. This flap, approximately

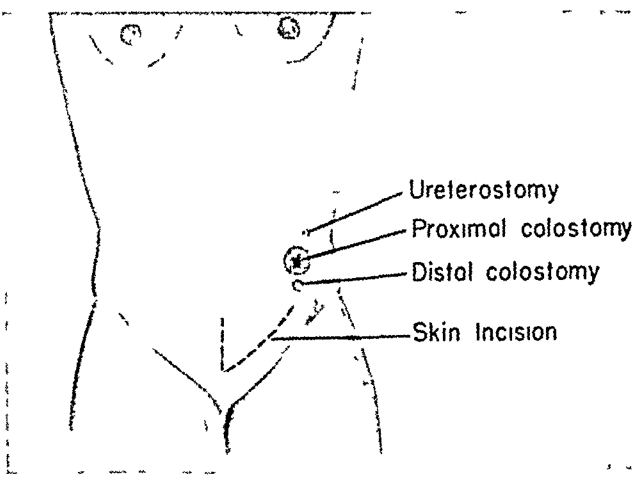

FIG. 2 Incision in skin and position of ureterostomy in relation to proximal colostomy

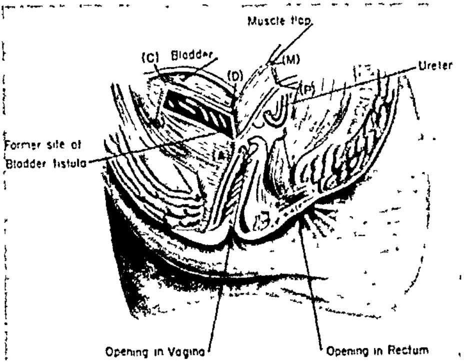

FIG. 3. Fistulous tract has been excised. Former site of vesical fistula is indicated just above *A*. *B* and *C* mark incision in dome of bladder. *C* and *D* and *A* and *B* mark parallel incisions which were made to form flap, *A*, *D*, *M*. *P*.

3 inches wide, was easily made by making the incision (fig. 3, *C* and *D*) parallel to *A* and *B*, figure 3. The mucous membrane was removed. All edges of the flap showed good blood supply. The defect in the bladder was closed by approximating side *A* and *B* to *C* and *D*, figure 3 with interrupted No. 00 chromic catgut. The flap was secured in such a way that it separated the suture lines in the bladder, vagina and rectum (fig. 4). The lower end of the left ureter was markedly thickened over a distance of approximately 10 cm. It was felt that this thickening rather than a stenosis of the ureterofistulous opening had caused the increasing hydronephrosis and attacks of pyelonephritis; therefore, it seemed reasonable to do a skin ureterostomy and later remove the kidney rather than do a ureteroneocystostomy. A No. 10 whistle-tip soft rubber catheter was passed up to the right ureter and brought out through the urethra. After closure of the abdominal wound the catheter which had been led up the right ureter was sutured to a labium and a Foley catheter was introduced into the bladder. The ureteral

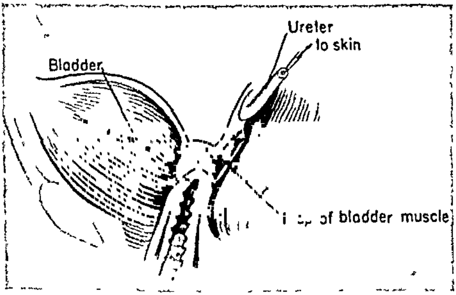

FIG. 4. Opening in rectum, vagina and bladder closed. Bladder flap has been used to separate closures.

catheter was left in for 9 days and drained most of the urine from the right kidney. Postoperatively the patient did well and the repair remained closed.

The left kidney and ureter were removed in October 1950. The patient has been seen at 4-month intervals to the present date and she has remained in good health.

The drawings were made by Dr. Jorge Rodrigues-Arroyo.

COMMENT

Many operations have been designed to close openings between the bladder, vagina and rectum. Some of these are simple in design and work well. There are some repairs, expecially in patients who have received large amounts of irradiation, which are difficult to close successfully. It is for such cases that the operation described may be helpful.

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URETEROSIGMOIDOSTOMY COLLECTIVE REVIEW OF RESULTS IN 2897 REPORTED CASES

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In 1936, Hinman and Weyrauch reviewed collected experience with the technique and results of ureterosigmoidostomy and defined the basic principles of technique then in use

Several methods of ureterosigmoidostomy have continued to have wide acceptance The muscularizing principle is typified by the Stiles operation (fig 1) The distal ureter is buried in a tunnel-like fold of mucosa after introduction of its end into the bowel through a stab incision The Coffey 1 operation (fig 2) exemplified what Hinman and Weyrauch classified as a tunnel type of operation The direct type of anastomosis has recently been refined by Nesbit (fig 3), Cordonnier (fig 4) and others Recently a new principle, that of combining the tunnel principle with an elliptical end to side anastomosis (fig 5) has been used (Leadbetter, Weyrauch and Young)

In recent years, better methods of anesthesia, blood and fluid replacement, intestinal intubation and antibiotic therapy have permitted performance of more extensive operations and reduction in the need for staged procedures A clearer understanding has developed of disturbances in electrolyte balance which may occur after diversion of urine into the bowel We have undertaken another collective review summarizing 2897 cases in which ureterosigmoidostomy was done using one of the four major modifications of technique described Data for each type of operation have been analyzed with reference to hospital mortality, infection, pyelographic results, an reflux from bowel into upper urinary tract, and hyperchloremic acidosis

Table 1 indicates hospital mortality rates after ureterosigmoidostomy, with or without cystectomy, ranging from 13.6 to 25.5 per cent for the various types of operation The wide variation among different groups of cases makes comparison difficult Some tendency has been evident in recent years toward lowering of mortality Increasing experience with ureterointestinal transplantation and improvement in techniques appear to have more than offset assumption of less favorable operative risks

Table 2 compares the mortality rates for ureterosigmoidostomy in the absence of malignant disease and those for operations done as an adjunct to cancer surgery Ureterosigmoidostomy in a good risk patient without the superimposed hazard of pelvic cancer surgery appears to be a relatively safe operation Considerable variation in statistics is evident

Table 3 suggests that clinically recognizable pyelonephritis is relatively infrequent after the combined type of operation Experimental evidence (Wood-

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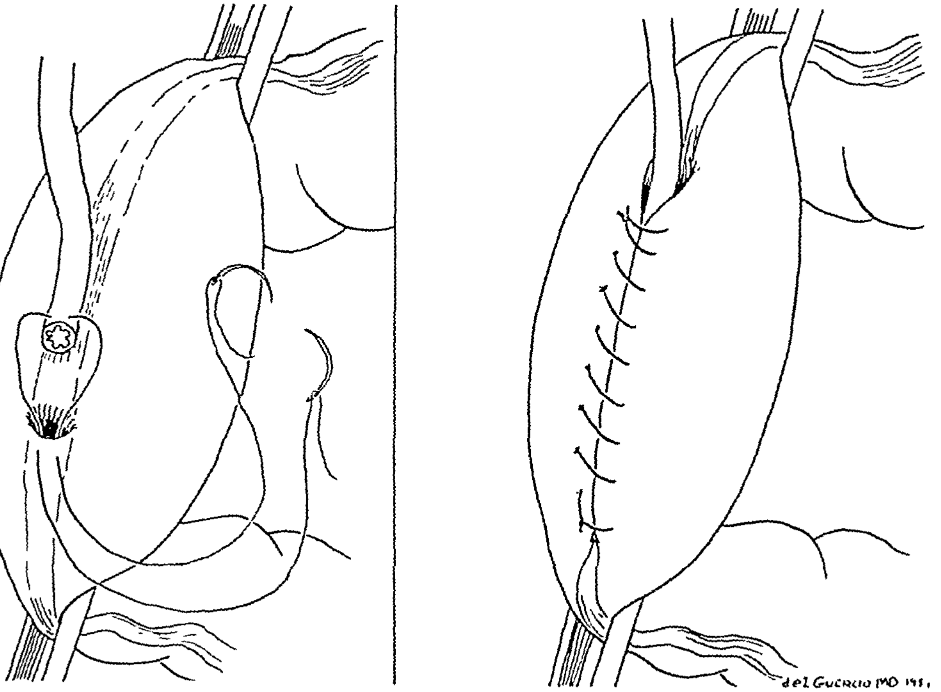

FIG. 1. Ureterosigmoidostomy: muscularizing principle. (Redrawn after Stiles.)

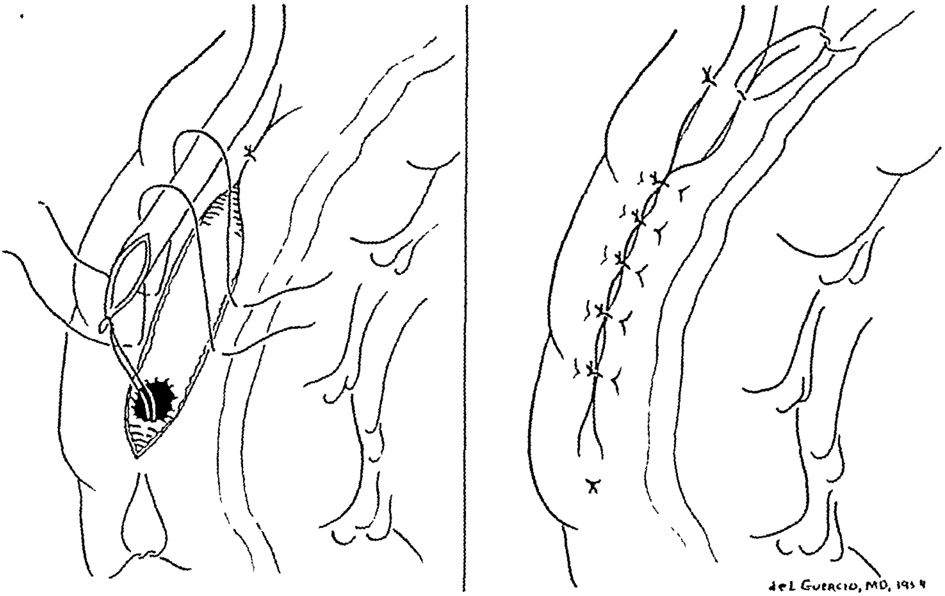

FIG. 2. Ureterosigmoidostomy: tunnel type of operation. (Redrawn after Coffey, 1911.)

ruff, Cooper and Leadbetter; Weyrauch and Young) suggests that the submucosal tunnel acts as a valve to prevent reflux of bowel contents into the ureter. The relatively high frequency of kidney infection (table 3) and the relatively common occurrence of air reflux (table 8) after the direct type of transplantation are probably related phenomena. After the Coffey 1 type of operation, granuloma formation or stenosis about the intraluminal ureteral stump has been shown experi-

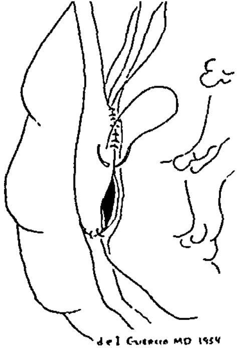

FIG. 3. Ureterosigmoidostomy: elliptical end to side anastomosis. (Redrawn after Nesbit.)

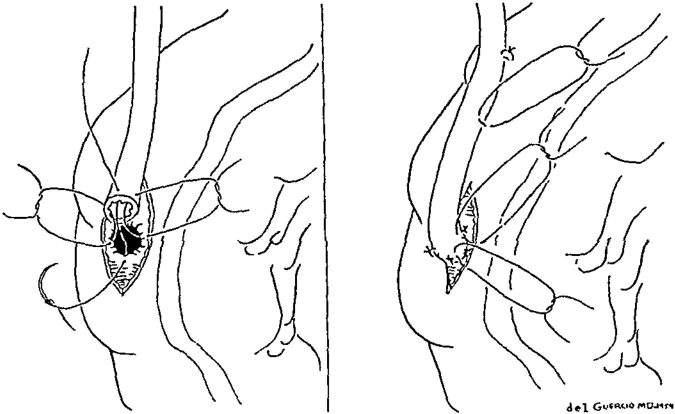

FIG. 4. Ureterosigmoidostomy: direct end to side anastomosis. (Redrawn after Cordonnier, 1950.)

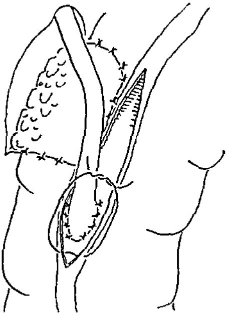

FIG. 5. Ureterosigmoidostomy: combination of tunnel principle with elliptical end to side anastomosis. (Redrawn after Leadbetter and Clarke.)

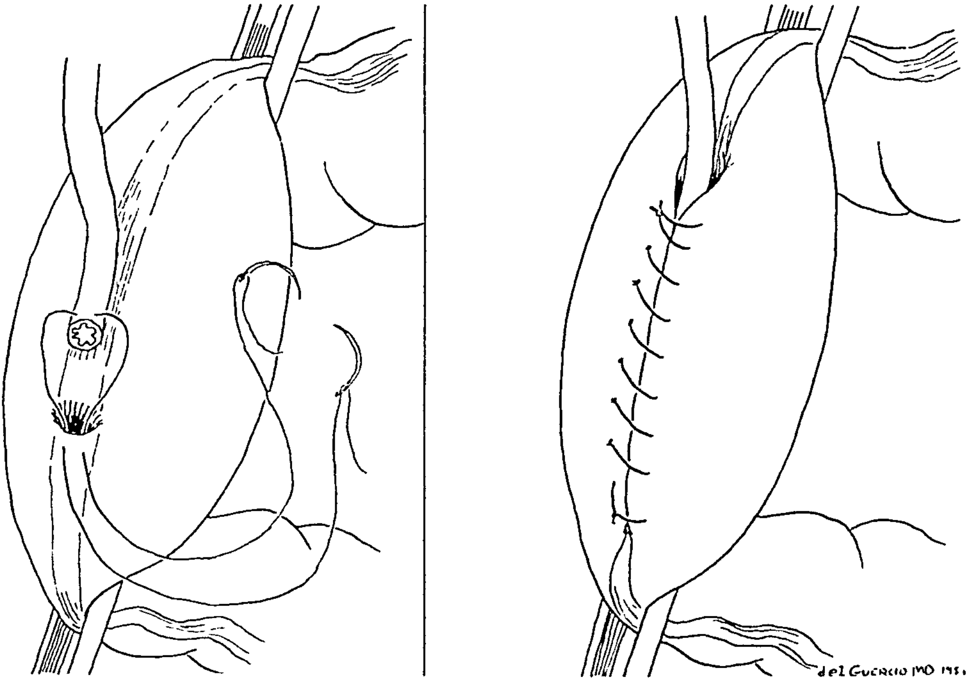

FIG. 1. Ureterosigmoidostomy: muscularizing principle. (Redrawn after Stiles.)

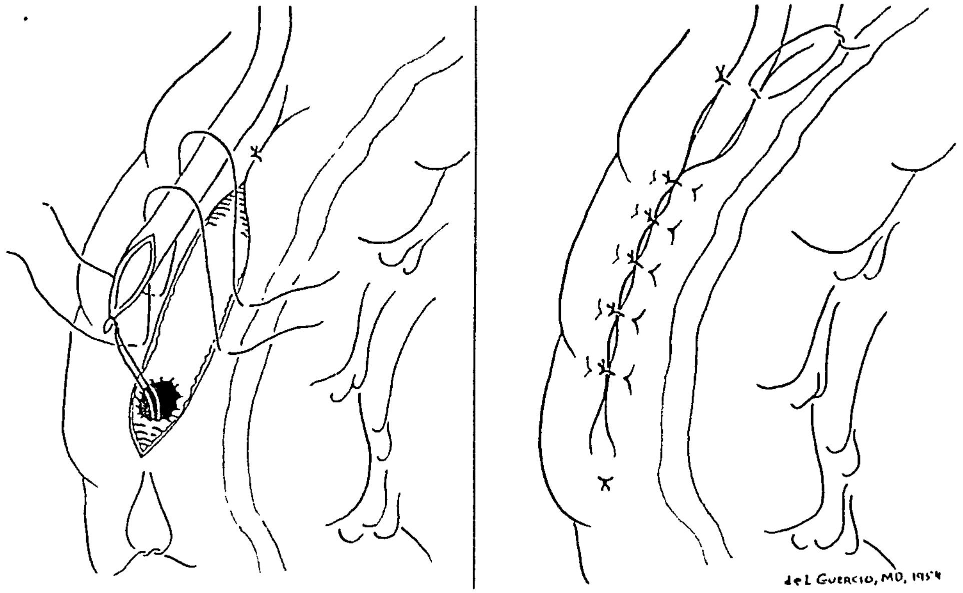

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TABLE 2 *Mortality rates ureterosigmoidostomy alone compared with ureterosigmoidostomy and pelvic cancer surgery*

Type of Operation	Number Cases	Hospital Deaths	%
With cancer operation, 1 or more stages			
Hinman and Weyrauch 1936	230	115	50 0
Smith 1947	17	12	26 5
Marshall 1947	104	13	12 5
Ferris and Priestley 1948	99	12	12 1
Colby 1952	116	20	17 0
Leadbetter and Clarke 1954	28	1	14 6
All reports	624	176	28 2
Ureterosigmoidostomy without cancer surgery for exstrophy of bladder			
Gross 1953	54	0	00 0
Higgins 1950	63	3	4 8
Harvard and Thompson 1951	144	18	12 5
For exstrophy and other benign or malignant disease but without pelvic cancer surgery			
Hinman and Weyrauch 1936	490	98	20 0
Smith 1947	17	0	00 0
Leadbetter and Clarke 1954	12	2	16 6
All reports	*780*	*121*	*15 5*

TABLE 3 *Incidence of nonfatal, clinical pyelonephritis after ureterosigmoidostomy*

Type of Operation	Number Cases	Pyelonephritis	%
Muscularizing operation			
Hinman and Weyrauch 1936	136	49	36 0
Tunnel			
Hinman and Weyrauch 1936	259	71	27 4
Schnittman 1948A	108	8	7 3
* Harvard and Thompson 1951	69	48	69 6
All reports tunnel operation	572	176	29 0
Direct anastomosis			
Cordonnier and Lage 1951	48	21	43 8
Combined operation			
Leadbetter and Clarke 1954	34	4	11 8

* The patients studied by Harvard and Thompson were observed over a longer period than those in other series tabulated

TABLE 4. *Known deaths from renal causes after ureterosigmoidostomy*

Type of Operation	No Cases	Deaths	%
Tunnel			
Smith 1947	64	9	14.0
Harvard and Thompson 1951	144	27	18.8
Colby 1952	96	15	15.6
* Jacobs and Stirling 1952	1322	246	18.6
Whitmore and Marshall 1953	168	18	10.7
All cases	1794	315	17.5
Direct anastomosis			
Jacobs and Stirling 1952	351	58	16.3
Combined operation			
Leadbetter and Clarke 1954	40	0	00.0

* Data include patients operated on by the muscularizing as well as tunnel techniques.

TABLE 5. *Final anatomic result after ureterosigmoidostomy*

Cases are tabulated as normal in which both kidneys and ureters appeared normal in pyelograms after operation, or in which one kidney was removed or one ureter ligated and the remaining upper urinary tract appeared normal after operation. A few are included in which death occurred before pyelograms were made but autopsy disclosed normal upper urinary tracts.

Type of Operation	Cases Studied	Cases Normal	%
Tunnel			
Jewett 1944	20	8	40.0
Schnittman 1948B	12	7	63.0
Harvard and Thompson 1951	41	5	12.2
Leadbetter 1953	23	9	39 0
All reports, tunnel operation	96	29	30.2
Combined			
Garrett and Mertz 1954	4	4	100.0
Leadbetter and Clarke 1954	37	24	64.9
All reports, combined operation	41	28	67.3

by Leadbetter and Clarke. This small group of patients was followed with the purpose of instituting external urinary drainage by nephrostomy or ureterostomy before renal disease had progressed to a degree immediately jeopardizing survival.

Tables 5 and 6 list the final results obtained after ureterointestinal transplantation. The relatively favorable figures for the combined operation corroborate the experimental inferences of Weyrauch and Young and of Woodruff, Cooper, and Leadbetter that the tunnel acts to prevent reflux while the elliptical mucosal anastomosis minimizes granuloma and stricture formation. Reflux could explain hydronephrosis when it is encountered after direct anastomosis, granuloma or stricture formation hydronephrosis after the tunnel and muscularizing procedures Increasing experience has shown that in performance of tunnel and combined types of operation generous muscular flaps should be fashioned to allow the ureter to lie loosely within the tunnel

TABLE 6 *Pyelographic results individual ureterointestinal implants*

Results are listed as normal only if the upper urinary tract remained normal or became normal after operation, with the exception of the data of Graves and Buddington which include some instances in which minimal hydronephrosis appeared after operation In other series, instances in which minimal hydronephrosis appeared are excluded from tabulation

Type of Operation	Number X rayed	Number Normal	%
Tunnel			
Schnittman 1948A	216	82	37 9
Schnittman,1948B	21	17	81 0
Graves and Buddington 1950	74	39	53 0
Garrett and Mertz 1954	9	4	44 5
All reports, tunnel operation	320	142	44 3
Direct			
Nesbit 1949	10	8	80 0
Cordonnier 1954	91	41	45 0
All reports, direct anastomosis	101	49	48 4
Combined			
Garrett and Mertz 1954	8	8	100 0
Leadbetter and Clarke 1954	67	43	64 0
All reports, combined operation	75	51	68 0

TABLE 7 *Incidence of x ray evidence of reflux of air from bowel into urinary tract after ureterosigmoidostomy*

Type of Operation	Cases Studied	Air Reflux	%
Tunnel			
Parks 1951	27	0	00 0
Marshall 1954	250	0	00 0
All reports, tunnel operation	277	0	00 0
Direct			
Cordonnier and Lage 1951	54	5	9 3
Parks 1951	9	6	66 7
All reports, direct anastomosis	63	11	17 5
Combined operation			
Leadbetter and Clarke 1954	35	0	00 0

TABLE 8. *Incidence of chemical evidence of hyperchloremic acidosis after ureterosigmoidostomy*

Type of Operation	Cases Studied	Hyperchloremic Acidosis	%
Tunnel operation			
Jacobs and Stirling 1952	80	26	32.5
Direct			
Cordonnier and Lage 1951	21	14	67.0
Jacobs and Stirling	121	55	45.5
All reports, direct anastomosis	142	69	48.5
Combined operation			
Leadbetter and Clarke 1954	20	6	30.0

TABLE 9. *Correlation of pyelographic findings after ureterosigmoidostomy with postoperative blood biochemical studies (20 cases)*

Result	No Biochemical Disturbance	Hyperchloremic Acidosis
Excellent (normal upper urinary tract)	11	0
Good (slight but appreciable persistent hydronephrosis)	2	4
Fair (moderate to severe persistent hydronephrosis but good dye excretion in pyelograms)	0	1
Poor (failures)	1	1

Table 7 indicates that air reflux from bowel into the upper urinary tract, seen by x-ray, is infrequent if it occurs at all after the tunnel or the combined types of operation.

A number of factors have been recognized as playing a part in the production of hyperchloremic acidosis after ureterosigmoidostomy. Among these are 1) selective electrolyte excretion and absorption by the bowel (Doroshow; Ferris and Odel; Eisman and Bricker; Mitchell and Valk; D'Agostino, Leadbetter and Schwartz); 2) bacterial decomposition of urea to form ammonium ions resorbed from the bowel lumen (Boyce and Vest); 3) pyelorenal backflow (Whisenand and Moore); tubular insufficiency (Kekwick, Paulley, Riches and Semple; Lapides).

The observations of Lapides, of Odel, Ferris and Priestley and of Creevy and Reiser suggest that poor renal function is commonly accompanied by hyperchloremic acidosis but that good kidneys appear able to compensate for the presence of urine within the bowel. Comparison of data from the literature (table 8) indicates high incidence of hyperchloremic acidosis after ureterosigmoid transplantation by any type of operation.

Table 9 summarizes 20 cases studied by Leadbetter and Clarke. Patients in whom the upper urinary tract remained pyelographically normal after operation did not show biochemical abnormalities. If even slight hydronephrosis developed, hyperchloremic acidosis proved relatively common. Among 6 patients who developed hyperchloremic acidosis there were 3 in whom one kidney was normal and the other only slightly dilated Each of the 6 patients showing hyperchloremic acidosis also exhibited azotemia at some time during their course In 3 patients the azotemia disappeared during correction of acidosis and hyperchloremia under treatment

SUMMARY

The results of 2897 collected cases in which ureterosigmoidostomy was performed are analyzed Four types of operation are considered 1) muscularizing operation, 2) direct anastomosis, 3) submucosal tunnel operation, 4) a combination of submucosal tunnel with direct ureterointestinal anastomosis

Operative mortality varied widely among groups of cases, but ureterosigmoidostomy appeared to be quite safe when not combined with pelvic cancer surgery

Pyelonephritis was less common after the combined operation than after other types

Hydronephrosis was less common after the combined operation

Air reflux from bowel into the ureter was seen by x-ray in 17 5 per cent of cases of direct anastomosis It was not observed after tunnel or combined types of operation

Hyperchloremic acidosis occurred in about a third of cases irrespective of type of operation Analysis of a small group of patients operated on by the combined technique indicated that this complication did not occur in the presence of a postoperatively normal upper urinary tract

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SURGICAL INJURIES OF THE URETER AND BLADDER

WM. NILES WISHARD, JR.

Ever since Simon[1] did the first nephrectomy in 1869 (for uretero-abdominal fistula) the literature has been replete with instances of surgical injury of the ureter and bladder. Why then, should anything more be said about it? Because, although attention has been called again and again to ureteral and bladder injuries resulting from pelvic operations, the incidence continues unabated and little has been done to prevent it.

Surgeons do not take too kindly to the prophylactically anchored ureteral catheter because it is not easy to palpate, particularly if adjacent tissues are indurated or fibrotic. Nevertheless, it has been found by Sisk (quoted by Moore[2]) that routine use of ureteral catheters before hysterectomy has practically stopped accidental ureteral injury. The prevention is so simple[3] and the cure so complex that it is strange this routine is not more widely used.

The ureter, so rarely injured by external trauma, is, because of its close relationship to pelvic organs, wittingly or unwittingly clamped, cut, severed, sectioned, tied, sutured or otherwise damaged with amazing frequency. It is a truism to say that it is ofttimes tied without the operator's knowledge, or development of subsequent symptoms or morbidity. Obviously there is no way of determining the frequency of this type of injury. Known injury, however, occurs with 2.42 per cent incidence in major gynecological surgery and 30 per cent in the Wertheim operation.[4] The purpose of this report is to deal with surgical injuries which have come to our attention.

URETERAL INJURY

In the last 5-year period we have treated 8 patients for inadvertent surgical injury of the ureter. One of these, a man, had a clamp momentarily placed on the ureter during the course of a combined abdominal perineal operation. The clamp was removed and no special treatment given. The patient subsequently had a normal convalescence and normal excretory urogram. Such an injury, trivial though it may seem, has resulted in fistula or stricture with sufficient frequency that some authors[1] advocate the use of a postoperative ureteral catheter. This momentary clamp type of trauma represents the least serious injury we have encountered.

The 7 remaining ureteral injuries in this series have been more complex. Two had ureters severed unwittingly in the course of a pelvic operation. The proximal

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Read at annual meeting, North Central Section of American Urological Association, Detroit, Mich. October 7–9, 1954.

[1] Aschner, P. W.: Accidental injury to ureter and bladder. J. Urol., 69: 774, 1953.

[2] Moore, T. D.: The management of surgically traumatized ureter. J. Urol., 59: 712, 1948.

[3] Patterson, J. H.: Ureteral injuries in pelvic surgery. Trans. South Central Sect. of Amer. Urol. Assn. 1952, p. 29.

[4] St. Martin, E. C., Trichel, B. E., Campbell, J. H. and Locke, C. M.: Ureteral injuries in gynecologic surgery. J. Urol., 70: 51, 1953.

untied ends were left to drain in the retroperitoneum with resultant abscess formation that necessitated ultimate nephrectomy. Two others had lower ureteral injury which resulted in ureterovaginal fistulas, one of which was also complicated by a vesicovaginal fistula. The fifth patient was one who, in the course of a complete hysterectomy, had both lower ureters efficiently tied and multiple vesicovaginal fistulas. The sixth had bilateral ureteral ligation as a result of a vaginal hysterectomy. The seventh had unilateral ligation incidental to bowel resection.

Let us look first at the ureter which is severed and allowed to drain in the retroperitoneum. One of these 2 patients was a woman of 29 who had previously had an appendectomy and right salpingo-ophorectomy, and a subsequent removal of the remaining pelvic organs in three different sittings by the same surgeon. Her complaint at each hospital admission was pain in the left side together with urinary frequency and burning. Each time pyuria was present but no investigative work was done. A fourth time she turned up in the hands of the same surgeon. In spite of her previous operations a diagnosis was made of appendicitis. At the fourth operation the appendix was of course absent, and so for that matter was everything else, but with great diligence a tubular structure was finally located on the left side deep in the pelvis which was presumed to be a fallopian tube. Because of its inaccessibility (it was really behind the peritoneum) a diagnosis was made of chronic inflammation and several inches of this tubular structure removed. The remaining proximal end was not tied. Immediate postoperative section showed that the structure was a ureter. At the end of 24 hours, under some duress, urologic consultation was requested. Immediate cystoscopy showed occlusion of the extreme lower end of the left ureter. X-ray showed a staghorn stone in the left renal pelvis, doubtless of long standing. The right kidney was normal. A left nephrectomy was done and a drain placed well down to the bony pelvis through the loin. This proved to be inadequate so that the retroperitoneal pelvic accumulation of urine subsequently had to be drained. The patient recovered, remarried and died 2 years later of hypertension with azotemia. The removed left kidney revealed extensive pyelonephritis as well as a staghorn calculus. It was presumably the cause of her illness from the beginning.

Case 2, a woman aged 30, had a pelvic operation elsewhere, the details of which were not available. A postoperative "cyst" developed in the lower abdominal wall. She consulted another surgeon who drained a retroperitoneal "cyst" containing 2 gallons of urine. Urologic examination revealed a functionless, infected, large left hydronephrosis, removal of which resulted in the patient's restoration to health. The lower ureter had been damaged in some manner so that the urine drained behind the peritoneum with resultant abscess. The damaged ureter plus the subsequent periureteritis and abscess caused the hydronephrosis. More prompt attention would probably have saved this kidney.

Now let us examine the 2 patients with ureterovaginal fistulas following hysterectomy for benign pelvic disease. One, a woman 58 had had an attempt to close an associated vesicovaginal fistula from below too soon after it was produced with resultant failure. Excretory urography, which should never be relied upon as the sole diagnostic procedure, demonstrated a normal upper tract. An additional unsuccessful attempt was made to close the fistula by intravesical repair Then a ureterogram, made by injecting the ureter from below, showed that there was also a ureterovaginal fistula Because of the patient's age and desire to minimize the number of operations, the kidney was removed and the remaining vesicovaginal fistula closed by suprapubic repair Three operations here could have been eliminated by a pair of anchored ureteral catheters at the time of the original operations

The second patient with ureterovaginal fistula was 56 She had had vaginal leakage of urine for 3 years following total hysterectomy Five days after operation the surgeon attempted to stop this leak by vaginal repair of a fistula Two serious errors were thus perpetrated: 1) the closure should not have been attempted this soon after formation of fistula, and 2) no fistula should ever be closed without adequate preliminary diagnosis to determine its exact location The old trick of giving blue dye by mouth, vein, or intravesical injection proves nothing except that a urinary fistula is present, a fact already embarrassingly apparent to the patient

The minimum urologic investigation should include

1) Careful history concerning urinary leak

2) Careful physical examination with special reference to tenderness in either renal fossa and palpability of the kidneys

3) Careful vaginal examination, bimanual and with speculum, to determine the location of the vaginal end of the fistula as well as any other coincidental abnormality At this time indigo carmine may be given intravenously or methylene blue injected intravesically

4) Careful cystoscopic and urethroscopic examination to orient the intraurinary end of the fistula with especial reference to its relationship to ureteral or vesical orifice

5) Upper tract investigation by a) ureteral catheter specimens to determine presence or absence of infection, b) differential function test, and c) urogram of the kidneys, ureters and bladder and perfect pyeloureterography to determine the existence of hydronephrosis or ureterovaginal fistula This last can be done best by holding a Braasch bulb to the ureteral meatus and injecting with 20 per cent skiodan following which an x-ray is made The bladder should be empty, or nearly so

If these precautions had been taken no vaginal operation would have been attempted on the patient of whom we are speaking The repair made 5 days after hysterectomy of course did not hold Undaunted, the surgeon made another attempt in 7 weeks with customary failure The patient despaired for 3 years She had become so accustomed to wearing a urinary poultice that she had forgotten what it was to be dry A friend advised her to have another try

This time cystoscopy was done It revealed no abnormal opening in the bladder A catheter would not pass through the intramural portion of the left ureter Excretory urography showed a large left hydronephrosis Methylene blue in the bladder did not appear in the vagina, although a urinary leak was observed during this time A left nephrectomy, with removal of a badly damaged hydro untied ends were left to drain in the retroperitoneum with resultant abscess formation that necessitated ultimate nephrectomy. Two others had lower ureteral injury which resulted in ureterovaginal fistulas, one of which was also complicated by a vesicovaginal fistula. The fifth patient was one who, in the course of a complete hysterectomy, had both lower ureters efficiently tied and multiple vesicovaginal fistulas. The sixth had bilateral ureteral ligation as a result of a vaginal hysterectomy. The seventh had unilateral ligation incidental to bowel resection.

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VESICAL INJURY

Coming now to surgical injuries of the bladder incidental to extraurinary operations we have found that a large vesicovaginal fistula occurs most often in those hysterectomies in which the cervix is removed with the uterus. We do not mean to use this as an argument for leaving the cervix, but rather to indicate that where cervical removal is contemplated it is even more necessary to exercise extreme caution in keeping away from the posterior wall of the bladder or trigone.

We have encountered 6 vesicovaginal fistulas during the period covered by this paper. Five of these resulted from hysterectomy and one was therapeutic in the treatment of long standing vesical tuberculosis. Two of the 5 have been mentioned in a previous paragraph of this report. One of these healed spontaneously. The other, associated with ureterovaginal fistula, was successfully closed by suprapubic extraperitoneal retrovesical repair. The therapeutic fistula was closed in a similar fashion. The remaining 3 deserve special mention.

One, aged 46, had had a vaginal hysterectomy for fibroid 3 months previously. Vaginal seepage of urine ensued. Complete urologic study showed an entirely normal urinary tract except a fistula in the trigone which would admit a No. 16 catheter. Vaginal examination showed that it was high. The vesical and vaginal openings of the fistula were fulgurated once with a small electrode. The patient stopped leaking immediately. An 8 months' follow-up showed the bladder healed, the vagina dry and the patient with normal vesical function.

A similar example was a woman 41 who 6 months previously had a supravaginal hysterectomy for laceration. Partial vaginal leak of urine followed. Outpatient examination showed a size 8F fistula in the midline at the upper margin of the trigone. A Bugbee electrode was thrust through the fistula so that its exposed tip was just in the vagina. Light coagulating current was applied and the electrode slowly withdrawn into the bladder. This was repeated twice more in 3 weeks. The patient became dry and remained so. Cystoscopy 4 months later showed a healed, epithelialized dimple on the upper margin of the trigone.

The final example of vesicovaginal fistula was found in a waitress 40 years old. At the age of 15 she had a midline appendectomy. At the age of 39 her left tube and ovary were removed. Six months later the right tube, ovary and uterus came out. Both these operations were midline. She then had a partial vaginal urinary leak. Five months later it was repaired elsewhere suprapubically. After 23 days of dryness, a total urinary leak developed. One month later cystoscopy showed a large fistula occupying more than half the space between each ureteral orifice. The ureters were normal.

Four months after the first repair a second closure was made by suprapubic, retrovesical, extraperitoneal approach. The catheter was allowed to drain 16 days during which time the patient was dry. She remained so after it was removed. One month later she reported that she thought there was a little vaginal nique of irrigation consisted of the passage of a 16 or 18F catheter, emptying the bladder and flushing out any gross debris with normal saline. Sixty cubic centimeters of clorpactin 90 (0.2 per cent) were then instilled into the bladder and left for 1 minute. The bladder was then emptied and a fresh charge of 60 cc of clorpactin solution was instilled. This was emptied after 1 minute. Further instillations of 60 cc each were made, held 1 minute, and withdrawn, for a total of five such interchanges. After the last instillation, the catheter was withdrawn and the patient voided the medication through the urethra. If the patient complained of discomfort at any time, irrigations were curtailed for that day, but were resumed after 3 days. If irrigations with clorpactin 90 were given daily, bladder irritation and even hematuria sometimes occurred.

SYMPTOMATIC IMPROVEMENT

Symptomatic improvement of tuberculous cystitis has been noted by most patients. Some patients whose bladders had been so tender that they had not been able to sit comfortably for many months were relieved of the discomfort after these treatments. As the tuberculous ulcers grew smaller, bladder capacities increased, although scarring and contractures of the bladder which had already become permanent were not changed. The last remnants of some ulcers did not disappear completely with local irrigations alone, pointing up the fact that this is a topical medication, with limitations. It is now being employed in combination with parenteral chemotherapy with streptomycin, PAS and isoniazid, as a valuable adjunct to therapy.

CASE ABSTRACTS

Case 1. Mrs. M. N., a 44-year-old white woman, had been voiding once every hour, day and night, for the past 3 years. She had been seen to have two ulcers in the dome of the bladder since left nephrectomy, 11 years previously. Eight months of chemotherapy with a combination of streptomycin, isoniazid and PAS had not yet produced healing of the tuberculous ulcers of the bladder. After three irrigations with clorpactin 90 the patient's symptoms were greatly relieved and she now finds it necessary to void only once at night, instead of every hour. Bladder treatments were continued for a total of 6 irrigations.

Case 2. Mr. J. U., a 33-year-old white man, had had a persistent tuberculous ulcer of the bladder for 3½ years, despite treatment with streptomycin and PAS. After 5 irrigations with clorpactin 90 his urinary frequency decreased from every 2 hours at night, to every 6 hours. Three tuberculous ulcers of the bladder were observed to decrease in diameter from 1 cm, to narrow lines 1 mm. in width, after 5 treatments (fig. 1). Irrigations were then continued at intervals of every 3 days for a total of 10 treatments. The linear remnants of the ulcers persisted, and chemotherapy with streptomycin and PAS will now be continued up to a total of 1 year.

Case 3. Mr. T. M., a 30-year-old Negro, had a severely diminished bladder capacity of 20 cc, and diffuse tuberculous cystitis without visible ulcers. He had a decrease in urinary frequency from 5 times during the night to once during the night, after 5 irrigations.

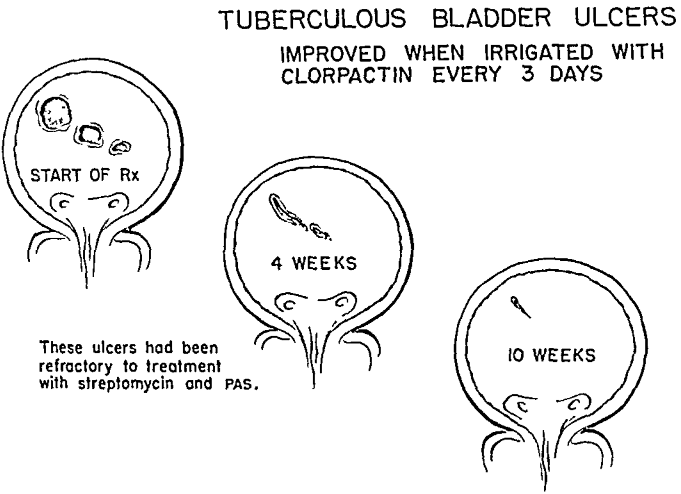
TUBERCULOUS BLADDER ULCERS
IMPROVED WHEN IRRIGATED WITH CLORPACTIN EVERY 3 DAYS
START OF Rx
4 WEEKS
10 WEEKS
These ulcers had been refractory to treatment with streptomycin and PAS.

FIG. 1. Bladder ulcer from case 2 had been present for 3½ years without improvement but showed improvement as soon as irrigations with clorpactin were started.

Case 4. Mrs. D., a white woman aged 51, had been unable to sit comfortably for at least 18 months, because of pain in the bladder due to severe tuberculous cystitis. The symptoms had begun after her nephrectomy for tuberculosis 2 years previously. Her bladder symptoms had not been relieved by 12 months of isoniazid, streptomycin and PAS therapy. These drugs had been given one after the other, rather than simultaneously, which may have accounted for their lack of effectiveness. After one irrigation with clorpactin 90 this woman's bladder pain disappeared and her urinary frequency decreased from 140 times in 24 hours to 8 times in 24 hours. Her bladder capacity has increased, and bladder irrigations will be continued at intervals, approximately twice weekly.

Nontuberculous cystitis is also benefited by bladder irrigations with this solution. Clorpactin 90 is an effective topical germicide which has been especially useful in patients where there was reflux to the kidney pelvis, so that the lumen of the entire urinary tract could be temporarily medicated. It kills B. proteus and Ps. aeruginosa on contact. It may also prove useful for Trichomonas and fungus infections of the vagina when used in preparations of a suitable pH.

INSTRUMENT STERILIZATION

Clorpactin may also prove useful for sterilizing instruments, cystoscopes or other hospital equipment which has been contaminated with tubercle bacilli. For this purpose another, a more economical grade, type 2DC, in a similar or more concentrated solution (usually 1 per cent) may be used. It causes no reaction on the chromium plated surface of cystoscopes, but ferrous or copper instruments should be washed after exposure to clorpactin lest a greenish film form on their surfaces. It should be washed from instruments with water, or neutralized with sodium thiosulfate (hypo) within a few minutes after removal from the clorpactin solution. Immersion in clorpactin 2DC for 30 minutes appears to kill M. tuberculosis on cystoscopes (preliminary data).*

SUMMARY

Clorpactin 90 is a new topical germicide of high potency which kills M. tuberculosis as well as other organisms. It has been helpful in healing cases of stubborn tuberculous cystitis. Some bladder ulcers which were refractory to streptomycin, isoniazid and PAS were seen to improve after bladder irrigations with solutions of clorpactin 90. It also has been helpful, to some extent, in nontuberculous cystitis due to B. proteus and Ps. aeruginosa, and clorpactin 2DC has been effective for the sterilization of instruments such as cystoscopes. Additional types of clorpactin are now being tested for increased effectiveness.

Clorpactin 90 is a chlorine derivative, solutions of which have detergent properties. It may be used for bladder irrigations. When used according to certain *strict specification it is an effective germicide.*

Acknowledgment is here made for the help given by Dr. William Steenken of the Trudeau Laboratories, who introduced us to this medication; and to Mr. Alfred Globus of the Guardian Chemical Company, of Long Island City, who provided the material for these experiments. We also wish to express our appreciation to our cystoscopic nurse, Mr. George Rosenblatt; to Dr. Michael Kenney and to Mr. Milton Goldman, our bacteriologists; and to our secretary, Miss Lillian Greenbaum, whose co-operation made this work possible.

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* Lattimer, J. K., Kenney, M. and Rosenblatt, G.: Clorpactin for sterilization of cystoscopes. Preliminary data, 1954.

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A STUDY OF THE HYPERACTIVE AUTONOMIC REFLEX INITIATED BY BLADDER DISTENTION IN PATIENTS WITH LESIONS IN THE CERVICAL AND HIGH THORACIC CORD

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Since the monumental studies of Head and Riddoch[1] [2] and Learmonth[3] it has been recognized that the distal stump of the transected spinal cord plays weird tricks on that part of the organism so unfortunate as to be innervated by it Being liberated, as it is, from all cerebral control the distal stump of such a spinal cord conducts its business in a most haphazard manner Sensory impulses, which in the normal patient would stimulate a segmental reflex response or a co ordinated motor response, may be transmitted throughout the entire distal stump of the transected cord stimulating somatic and autonomic motor neurons in a most alarming manner The most striking clinical manifestation of this phenomenon is mass involuntary peripheral muscle spasm which is sometimes powerful enough to throw the patient out of his wheelchair Such mass reflex response is not confined to the somatic nervous system, but also manifests itself through the autonomic nervous system Mass parasympathetic responses are observed in the bladder as bladder spasm and may be recorded in cystometrograms or by bladder electromyography Hyperactive reflexes of the sympathetic nervous system are manifest by vasoconstriction and by pilomotor and sudomotor responses of severe degree

These hyperactive reflexes assumed importance to the urologist when it was learned that under certain circumstances they are initiated by distention of the bladder In 1947 Guttman and Whitteridge[4] showed that in patients with lesions in the high thoracic or cervical cord, bladder distention caused severe headache, hypertension, bradycardia, and a pronounced sudomotor and pilomotor response These signs and symptoms disappear rapidly when the bladder is emptied It was also learned that this reflex could be abolished by drugs which block the parasympathetic nervous system (etamon),[5] by spinal anesthetic and by posterior rhizotomy [6] In addition to vesical distention the reflex can be initiated by rectal distention (enema)[7] and by stimulation of certain skin areas below the level of the lesion However, in most cases it is bladder filling that produces the most marked response

Subsequent studies revealed that this is a highly consistent finding in such cases and that it occurs in both complete and incomplete lesions It has been reported in lesions as low as D7 [4] The severity of the reaction varies from patient

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[1] Head, H and Riddoch, J Brain, 40 188-263, 1917

[2] Riddoch, J Brain, 40 264-402, 1917

[3] Learmonth, J R Brain 54: 147-176, 1931

[4] Guttman, L and Whitteridge, D Brain, 70 361-404, 1947

[5] Thompson, C L and Witham, A C New Eng J Med , **239** 291-294, 1948

[6] Bors, E A M A Arch Surg , **64** 803 1952

Schumacher, G A and Guthrie T C A M A Arch Neurol & Psychiat , **65** 568, 1951 to patient and sometimes one or more of the symptoms will be absent. Clinically, these patients do well as long as their bladders are kept empty. If the catheter becomes blocked, they may become acutely ill and experience severe headache and profuse sweating. The potential danger to life of the hypertension is readily apparent.

Filling the bladder of humans with normal spinal cords and with lesions below D7 does not reproduce these symptoms.[8]

The exact mechanism by which this reflex manifests itself is not determined. The bladder itself has two afferent pathways to the cord. One through the sacral parasympathetics and one through the hypogastric plexus (sympathetic). In addition to this, stimulation of the skin may also serve as the sensory stimulus and this must be mediated through somatic nerves. Of the possible afferent pathways the sacral parasympathetics must be the most important since a low spinal anesthetic blocks the reflex. There is also a debate as to the mode of transmission upward. The paravertebral sympathetic ganglia and plexus could do this, or the impulse could be transmitted through pathways in the cord itself. The latter seems more likely as mass peripheral spasm commonly accompanies this reflex indicating stimulation of the anterior horn cells within the cord. The efferent pathways seem to be sympathetic and manifest themselves in vasomotor, sudomotor and pilomotor responses. The hypertension is thought to be due to vasospasm in the visceral vessels due to splanchnic stimulation. It is awesome indeed to contemplate that a stimulus so commonplace as a spurt of urine through the ureteral orifice could initiate such a wild, uncontrolled reaction through the entire distal stump of the spinal cord, involving motor neurons of all the three great nervous systems,* manifesting itself clinically in violent hyperactivity in diverse parts of the body, and all for the loss of cerebral inhibitory influences.

CASE REPORTS

Case 1. A. N., a 29-year old white man, sustained an incomplete lesion at C7 in December 1950. Examination revealed that his blood pressure rose from 95/55 to 170/105 when his bladder was filled to its capacity, which was 150 cc. Associated with this rise in blood pressure was a fall in pulse rate from 76 to 50 beats per minute. Bladder contractions became prevalent at 55 cc fill and continued as more fluid was introduced into the bladder. Severe leg spasms were made worse. At 100 cc of bladder fill large beads of perspiration appeared on the forehead and face, neck and arms. Pilomotor erections became evident on the arms and neck at 150 cc of bladder fill, and with the cystometrogram showing a passive pressure of 40 cc of H_2O, the bladder fluid began to leak back around the catheter. The patient did not get a headache but said that if his bladder were allowed to remain full for 30–45 minutes, he would get a severe headache. After his bladder was emptied his symptoms stopped and his pulse and blood pressure returned to normal.

In April 1953 (4 months after the aforementioned study) a complete rhizotomy

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[8] Robertson, H. S. and Wolff, H. G.: Arch. Neurol. & Psychiat., **63**: 52–55, 1950.

* Somatic, mass peripheral spasm; parasympathetic, bladder spasm and sympathetic, vasocontraction, pilomotor and sudomotor.

(from D10 to S5) was done in an effort to combat the spasm in his legs. Repeat examination 2 months later showed that his peripheral spasm and his bladder spasm were abolished. The bladder which originally held 150 cc now had a capacity of 400 cc. It could be filled to capacity without inducing any of the aforementioned signs or symptoms.

Case 2. F. C., a 36-year-old white man, received a complete cord lesion at C6 in January 1951. In April 1952, his bladder capacity was 200 cc with severe spasm and it was noted that filling his bladder caused him to sweat above the level of the lesion. In October 1952, his bladder capacity dropped to 100 cc with severe spasm and high passive pressure. As his bladder was filled, his blood pressure rose from 150/95 to 240/110, and his pulse rate dropped from 56 to 42. See figure 1. Sweating and pilomotor erection developed. The patient's peripheral

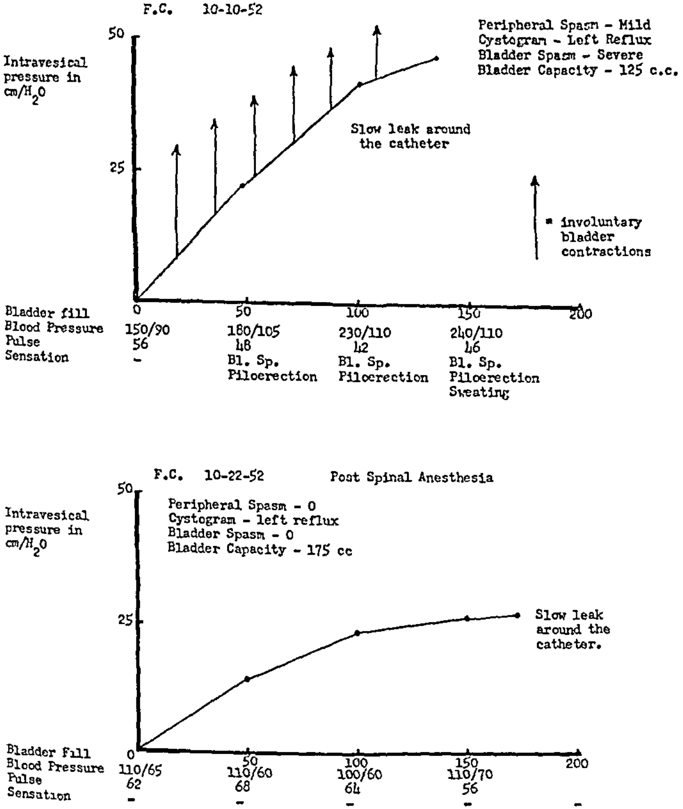

FIG 1

spasm was mild and he had no headache. Twelve days later this was repeated after a spinal anesthetic. His bladder capacity increased slightly to 175 cc. His bladder spasms were abolished and there was no change in blood pressure or pulse rate as the bladder filled. Pilomotor erections and sweating did not occur.

In August 1953, the patient was given an injection of absolute alcohol into the subarachnoid space. Six weeks later his capacity was 300 cc but 4 months post alcohol, the bladder capacity was back to 125 cc. However, all spasm, blood pressure, pulse changes, pilomotor erections and sweating were abolished.

Case 3. D. H., a 19-year-old white man, sustained a complete cervical cord lesion in September 1949. Three years later his bladder capacity was 100 cc with severe bladder spasm and peripheral spasm. His blood pressure rose from 140/90 to 215/140 and his pulse rate dropped down from 84 to 64 as the bladder filled At 75 cc his face began to sting and he noticed a metallic taste in his mouth. He began to sweat in the back of the neck and pilomotor erections developed. At 100 cc pain occurred in the bladder and right costovertebral angle, associated with nausea. These symptoms and signs disappeared when the bladder emptied.

The patient was given a low spinal anesthetic and the bladder was filled again. There were no changes in blood pressure or pulse rate. The only sensation noticed was pain in the bladder and in the right costovertebral angle. Because of this, the examination was discontinued after 125 cc had been instilled into the bladder.

Case 4. R. H., a 20-year-old white man, sustained a complete cord lesion at C7 in August 1949. One of his most disturbing clinical symptoms had been headache which started with bladder irrigations or a plugged catheter or with an enema. Extremely severe headache followed the removal of several bladder stones transurethrally. He was investigated in September 1952. His bladder capacity was 250 cc and bladder spasm began at 75 cc. His blood pressure was 120/75 with his bladder empty and it rose to 240/140 with 250 cc of fluid in his bladder. His pulse rate began at 78 and dropped to 52. Pilomotor erections and sweating occurred above the level of the lesion. No headache occurred during this examination but the patient said it would begin if his bladder remained full much longer. The following day a spinal anesthetic was administered and the test repeated. The bladder capacity was now 375 cc and this fluid was accommodated without any of the above noted signs or symptoms. Bladder spasm was completely abolished.

On October 1, 1952, this patient had a pelvic deinnervation, which was an effort to remove the segments of the sacral parasympathetics communicating with the bladder without sacrificing the peripheral nerves. The advantage of such a procedure is readily apparent. Its technical difficulties are equally apparent. Sixteen days after this operation, the bladder capacity was 350 cc. No spasm was encountered until 325 cc of fluid had been instilled into the bladder. He had no appreciable rise in blood pressure or drop in pulse rate until 300 cc had been instilled into the bladder. At the 300 cc point, the blood pressure rose from 115/75 to 160/100 and the pulse dropped from 100 to 76.

Six months later his capacity was 400 cc but his bladder spasms were more frequent and occurred as early as 150 cc. Blood pressure, pulse and pilomotor changes were not marked until 300 cc The patient said that his headache had been greatly reduced by the operation (pelvic denervation) but that he occasionally experienced his old type of headache with a very full bladder Now, however, they did not occur every time the bladder was full, and when they did occur, they were not so severe He also noted that his leg spasm was worse but his bladder spasm was much reduced and that his bladder held a lot more than it did previously

We felt that the pelvic denervation was incomplete and a subarachnoid alcohol injection was done This abolished his peripheral spasm and all signs and symptoms associated with bladder filling

Case 5 C W, a 23-year-old white man, sustained a complete cord lesion at C5–6 in June 1947 Check-up examination 5 years later revealed a bladder capacity of 300 cc with moderately severe spasm Blood pressure changes were not marked (100/60 to 135/85), nor were pulse rate changes (56 to 48) However, after 125 cc of fluid had been injected into his bladder, he began to perspire profusely on the left side of his face The right side remained perfectly dry This persisted throughout the duration of the test and rapidly disappeared when the bladder was emptied

Case 6 D B, a 15 year-old white boy, sustained a complete lesion of the cervical cord in July 1952 Examination 3 months later revealed a bladder capacity of 250 cc with no bladder spasm demonstrable on the cystometrogram Blood pressure and pulse were only slightly altered However, at 100 cc bladder fill he began to sweat profusely from the left side of the face, neck and left arm The right side remained dry This situation persisted to bladder capacity (250 cc) at which time both sides of the face became drenched in perspiration

The patient was out of spinal shock at the time of this examination as he had a return of deep reflexes and mild spasms in both legs and arms The case illustrates how early those changes occur

Case 7 L C, a 43-year-old white man, received an incomplete cervical lesion in June 1949 Examination 40 months later revealed a bladder capacity of 200 cc As the bladder filled, the blood pressure rose from 110/70 to 185/95 and the pulse rate dropped from 60 to 52 Bladder spasms developed at 50 cc, which continued to capacity His neck became moist at 100 cc At 150 cc, his face and neck were sweating and at bladder capacity, the perspiration was forming on the face, neck and arms, and pilomotor erections were forming over the arms and neck His bladder was emptied and all these signs and symptoms returned rapidly to normal

Case 8 R G, a 19-year-old white man, was injured in July 1950 He sustained an incomplete lesion of the cervical cord at C5 Examination 3 years later revealed a bladder capacity of 250 cc There were no spastic contractions until capacity was reached Filling the bladder caused no appreciable change in either the blood pressure or the pulse It was noted that when the bladder reached capacity and the involuntary emptying contraction occurred, pilomotor erections appeared on both arms

Case 9 W J, a 31-year-old white man, was injured in March 1951 He sustained an incomplete lesion at C5–6. He was examined 20 months later. His bladder capacity was 400 cc and bladder spasms were frequent and severe. The blood pressure rose from 100/65 to 205/110 and the pulse rate dropped from 60 to 50. There were no pilomotor erections and no perspiration but beginning at 250 cc fill, there was a blotchy, red rash which developed on the skin of the abdomen and chest. This disappeared along with the hypertension and bradycardia when the bladder was emptied.

Case 10. A. R., a 22-year-old white man, received a complete lesion of the cervical cord at C6–7 in January 1950. Examination 2½ years later revealed a bladder capacity of 300 cc with moderate bladder spasm. The blood pressure rose from 105/70 to 190/125 as the bladder filled. The pulse rate dropped from 64 to 44. At 150 cc the patient noticed a vague sensation in the face, arms and shoulders and he began to perspire slightly. At 250 cc the patient became nervous and apprehensive with muscle fasciculation in the arms. Sweating became heavy and headache began. The entire process stopped when the bladder was emptied.

DISCUSSION OF CASES

Ten cases have been presented in which this hyperactive autonomic reflex is demonstrated. In four of the cases efforts were made to stop the symptom complex either on a temporary or a permanent basis. In the first case this was accomplished with an anterior and posterior rhizotomy from D10 through S5. This operative procedure was done primarily to stop peripheral spasm, but it does afford an opportunity to observe the effect of such an operative procedure upon the autonomic reflex under discussion.

In the second, third and fourth cases, spinal anesthesia with novocaine stopped the reflex. In the second and fourth cases subarachnoid alcohol was used and this was also successful in abolishing the autonomic reflex. In the fourth case a surgical attempt to disrupt the parasympathetic nerves in the pelvis was partially successful in stopping this reflex.

In addition to the basic signs and symptoms of hypertension, bradycardia, headache, sudomotor and pilomotor responses, other phenomena were observed in this series in connection with bladder fill. These include nausea, nervousness, apprehension, metallic taste in the mouth, muscular fasciculation and stinging sensation in the face. Like the basic symptoms these cleared when the bladder was emptied. The case of D. B. was of interest as the patient was checked only 3 months after sustaining a complete cervical lesion and demonstrates how quickly the hyperactive autonomic reflex may occur following injury.

SUMMARY

A knowledge of this automonic reflex is of particular value to the urologist who may be called upon to evaluate the urologic status of patients with high lesions in the spinal cord, and to oversee their bladder training. In our clinic we have abandoned the use of tidal drainage in such patients. We have also become reluctant to remove their urethral catheters unless we are certain that the patient voids satisfactorily without headache, hypertension and sweating. Most of the

routine urologic diagnostic procedures involve bladder distention (cystoscopy, cystogram and cystometry) Since the bladder distention is only temporary in these instances we employ them as freely in the patients with high lesions as in the lower lesions and have encountered no adverse effects

Operative procedures which involve filling and emptying the bladder (transurethral cystolithotomy and bladder neck resection) can be safely employed in spite of this reflex mechanism Often the blood pressure will be high and fluctuating but we have encountered no serious complications from this If one wishes to abolish this reflex during an operation on the bladder, spinal or caudal anesthesia may be employed During any surgical procedure it is advisable to have the urethral catheter open so that the anesthetist will not become confused by the blood pressure recordings resulting from bladder distention

The desirability of surgical intervention to stop this reflex must be considered on the merits of the individual case The severity of symptoms must be weighed against the value of the nerve roots destroyed and the danger of the surgical procedure Dr Bors[6] found that posterior rhizotomy effectively abolished this reflex Subarachnoid alcohol is also effective but may not prove to be as permanent

An awareness of this autonomic reflex and of methods by which it may be abolished is of value not only from the therapeutic standpoint but also because it adds to our understanding of the general problem of cord injury patients and the part played by the distal stump of the spinal cord in the production of some of the bizarre clinical manifestations of spinal man

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TRIGONAL CURTAIN OBSTRUCTION IN A FEMALE CHILD

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Urogenital tract infections are universally recognized as a major cause of childhood morbidity. What is too often overlooked is the relative frequency of underlying obstructive urogenital congenital anomalies. These congenital obstructive anomalies may occur anywhere in the genitourinary tract. This paper is concerned with a rare obstructive lesion of the bladder, undoubtedly congenital in origin, and variously called trigonal curtain obstruction or redundancy of the trigonal mucosa.

Beer in 1924 described an 8½-year-old boy, suffering from chronic urinary retention, who at transvesical operation presented a "fold of mucous membrane close to the internal sphincter which acted as a valvular obstruction to the outflow of urine."

Campbell in 1932 described a case in a 15-month-old girl. At operation through the open bladder an obstructing curtain was seen to originate and hang from its attachment at the lateral trigonal borders and adjacent bladder wall. The ureteral orifices were deep in the sulcus behind the curtain and 1 cm. posterior. He called the lesion trigonal curtain obstruction of the bladder outlet and considered it to be the first reported case. In addition, Campbell cites six more cases Of these, three were incidental findings at postmortem studies and in three the diagnosis was made clinically.

Harris in 1933 described a 5-year-old girl who at operation presented a "cup-like, elevated, rather large fold of redundant mucous membrane with the concavity upwards lying transversely just behind the internal urethra and acting as a perfect cup-valve, shutting off the vesical neck."

The author's impression was that this was a congenital valve obstruction at the vesical neck. However, examination of figure 1 will reveal the similarity of this lesion to ours.

CASE REPORT

B. S. R., a 7-month-old white girl was admitted to the pediatric ward of the Maimonides Hospital on June 25, 1953 with a history of intermittent fever, irritability, anorexia almost since birth, dysuria and pyuria of 2 months' duration. Her prenatal history was noncontributory. Her delivery and development had been normal. Her 4-year-old brother and parents were alive and well. Recurrent febrile episodes with temperatures approximating 104F were treated by and responded to various antibiotics. These were attributed to upper respiratory infections.

At the age of 5 months she had a febrile episode which resisted antibiotics and was hospitalized for investigation. The blood urea nitrogen at that admission was 23 mg. per cent. The urine revealed marked pyuria. After several days her

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temperature returned to normal and the patient was discharged with a diagnosis of common cold

Three months later the patient's symptomatology recurred and the child was re-admitted Physical examination was negative A complete blood count revealed a hemoglobin of 9 1 gm per cent and 3,000,000 red blood cells The white blood cell count was 17,000 with a normal differential The urine was grossly cloudy, acid, and had a specific gravity of 1 004 There was 1 plus albuminuria and numerous white blood cells in clumps were present B coli were cultured from the urine and the organism was sensitive to all antibiotics The blood urea nitrogen was 25 mg per cent During this admission it was discovered that the child voided infrequently Examination on these occasions revealed a distended bladder which required catheterization and a large quantity of urine was obtained each time A flat film of the abdomen and a chest film were negative Several attempts at excretory urography were unsatisfactory Two successive cystoscopies utilizing a Butterfield catheterizing cystoscope rendered little information All one could discern was a congested bladder mucosa and a

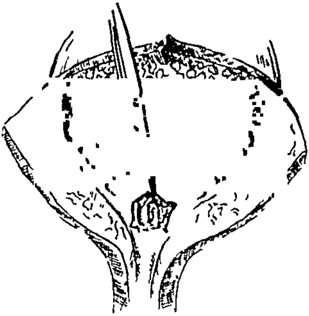

FIG 1

small diverticulum The ureteral orifices could not be identified at any time A cystogram revealed a large, distended bladder (fig 2, *A*) At a subsequent examination a Brown Berger 16F cystoscope was introduced into the bladder and both ureteral orifices were identified The bladder mucosa was markedly trabeculated and the trigone appeared to be elevated The bladder neck was hypertrophied and proximal to it a flap arising from the posterior wall of the bladder was seen (fig 3) The diverticulum was noted once again Both ureters were catheterized with 4F ureteral catheters and the urine specimens from both kidneys were cloudy Bilateral retrograde pyeloureterograms were taken (fig 2, *B*) The x ray report was as follows

"A plain film of the abdomen shows the tip of the cystoscope at the level of the umbilicus indicating tremendous distention of the bladder This is also seen after introduction of the contrast medium There was reflux of dye into both ureters, pelves and calyces The latter are dilated and clubbed The left ureter and, to a lesser degree, the right ureter, are tortuous, dilated and their distal portions are tapered "

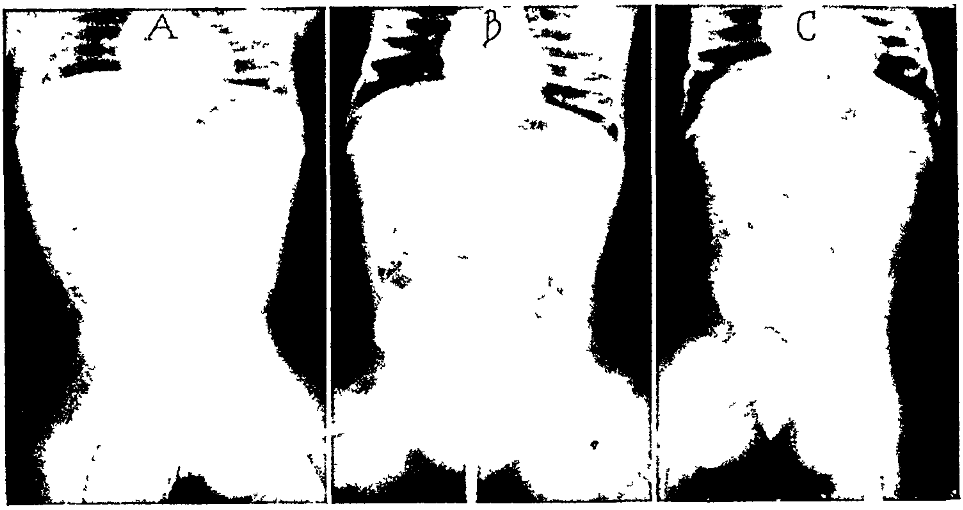

FIG. 2. *C*, cystogram with reflux of dye up both ureters. Photograph touched up for clearness.

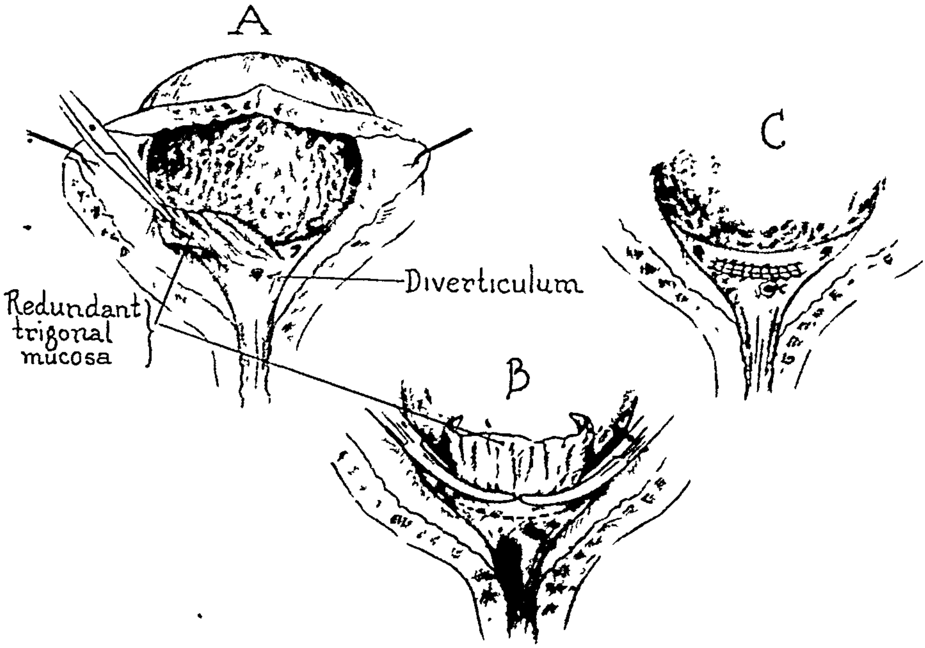

FIG. 3. *RDT*, redundant trigonal mucosa. *D*, diverticulum.
A, preoperative condition of bladder. *B*, redundant trigonal mucosa being excised. *C*, postoperative condition of bladder.

Surgery was advised and after preliminary preparation the child was operated on July 21 through a suprapubic incision. The bladder was opened at its lowermost portion. The trigone presented a fan-like apron with its base just below the ureteral orifices. The attached base measured 1 cm. wide and the free margin 4 cm. wide. Just distal to the base the small diverticulum exuded free pus. The apron was excised between the ureteral orifices which had been catheterized previously. The base was then sutured with No. 00 chromic catgut. The fundus of the diverticulum was everted and excised after ligation of its base. A dePezzer catheter was introduced for suprapubic drainage and the wound closed in layers. The space of Retzius was drained.

The child made an uneventful recovery and was discharged on the sixteenth day postoperatively. Unfortunately the dePezzer catheter fell out 4 weeks later and the suprapubic sinus was allowed to close spontaneously.

The child has had 4 readmissions for follow-up studies. She has been in good health and has been voiding normally. Her residual urine was 10 cc and cystoscopy 3 months postoperatively revealed no evidence of the trigonal curtain and the sutured area could not be distinguished. The right ureteral orifice was completely normal. The left ureteral orifice had a small arcuate fold on its superior aspect which did not obstruct the egress of urine. On the fourth and last admission, cystoscopy was repeated. The findings were similar to those of the previous cystoscopy except that for the first time it was noted that the patient had two right ureteral orifices. These were catheterized and a retrograde pyeloureterogram revealed complete reduplication of the right kidney (fig. 4, *A*). A review of the patient's x-rays reveals marked improvement in the appearance of both kidneys although the left ureter is still tortuous. However, admittedly the pelvicalyceal system is still far from normal (fig. 4, *B*).

EMBRYOLOGY

A review of the embryological development of the bladder and more especially of the trigone suggests that the "redundant trigonal curtain" is due to persistence of the fused portion of the urogenital sinus and mesonephric duct which exists during fetal life. During the development of the bladder and kidneys the terminal portions of the mesonephric ducts are absorbed into the bladder wall and this

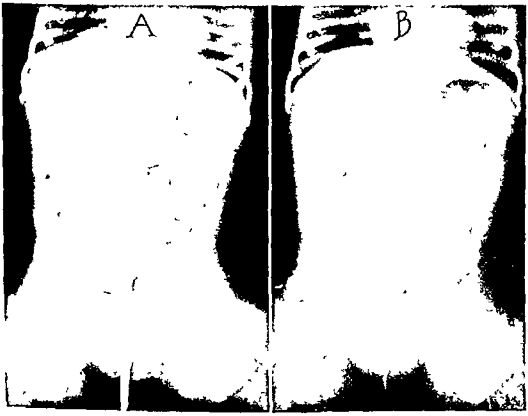

FIG. 4

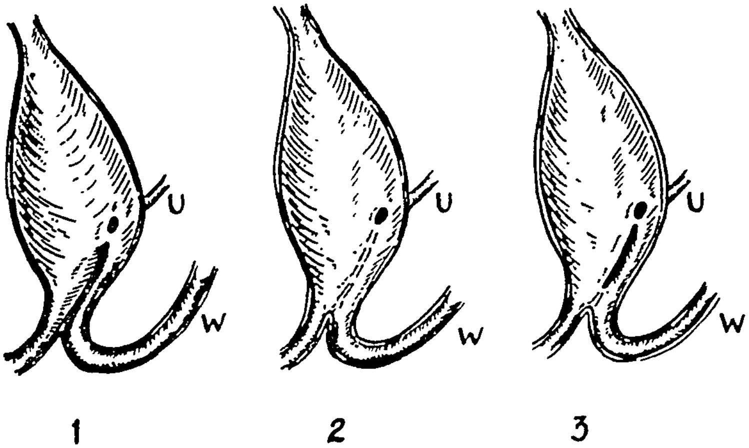

FIG. 5. U, ureter. W, mesonephric duct
1, Fusion of mesonephric duct with urogenital sinus. *2*, Disappearance of fused portion of mesonephric duct and urogenital sinus represented by dotted line. *3*, postulated failure of disappearance of fused portion of urogenital sinus and mesonephric duct except at its inferior portion.

continues until the mesonephric duct caudal to the point of origin of the metanephric diverticulum has disappeared. The end result is that the mesonephric and metanephric ducts open independently into the urogenital sinus. The metanephric duct acquires its opening lateral and cephalad to the opening of the mesonephric duct, a short distance away. This is the situation in a 17 mm. embryo. Subsequently, the openings of the mesonephric ducts assume a lower level and come to lie in the primitive urethra. The change of the level of the entry of the openings of the mesonephric ducts are brought about in the following manner (fig. 5).

Previously opening into the urogenital sinus near the ureters, the mesonephric duct on each side is folded down into a loop, fusing in front with the epithelial wall of the urogenital sinus so that it runs up embedded in this. This fused portion gives way (as is shown in the dotted line in figure 5, *2*) leaving ducts opening at a lower level in the primitive urethra. If one postulates failure of disappearance of the fused portion of the urogenital sinus and mesonephric duct except at its inferior portion (fig. 5, *3*) then it is obvious how a trigonal curtain may be formed.

Accordingly we submit that a more accurate name for this anomaly is "persistent urogenital mesonephric septum."

DISCUSSION

It is easy to see how such a structure caused mechanical intermittent obstruction of the bladder outlet with its ensuing bladder trabeculation, diverticulosis, hydroureter and hydropelvis. Early detection of such a condition would prevent irreversible damage to the renal parenchyma with consequent loss of life and once more emphasizes the necessity for early complete urological survey of obscure infection and chronic resistant pyuria in childhood.

The treatment is complete removal of the obstruction, however, this alone will not reverse the damage occurring to the proximal genitourinary tract caused by the obstruction A prolonged period of bladder drainage pre- and postoperatively is essential In our opinion suprapubic drainage is the most efficacious For this reason we feel that a transvesical route rather than a transurethral route should be used for the removal of the obstructing lesion

SUMMARY AND CONCLUSIONS

An additional case of trigonal curtain obstruction is presented The literature has been reviewed and an embryological explanation for the condition suggested On the basis of this, a more exact name has been submitted, i e , persistent urogenital mesonephric septum

Transvesical rather than a transurethral approach has been supported as the operative route of choice because this affords the more efficient mode of bladder drainage

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BENIGN NEOPLASMS OF THE URINARY BLADDER IN CHILDREN: REVIEW OF THE LITERATURE AND REPORT OF A CASE

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Neoplasms of the urinary bladder occur infrequently in childhood. When they do occur, they are very malignant and differ from the adult disease in that they are usually of mesothelial rather than epithelial origin. Benign tumors in children are extremely rare and though they may be benign from a histological standpoint, they nevertheless often prove clinically as lethal as malignant tumors causing uremia by interference with ureteral drainage and superimposed secondary renal infection leading to death.

The following case is reported because it represents a 6-year survival following conservative bladder surgery for a benign tumor of the urinary bladder.

CASE REPORT

A 7-year old boy was seen in urologic consultation because of a 2 weeks' history of intermittent, painless hematuria. Physical examination was negative for periorbital or peripheral edema. The fundi were negative on ophthalmoscopic examination. There was pallor of the mucous membranes. The heart and lungs were negative. The blood pressure was 100/60. The abdomen was soft. Neither kidney was palpably enlarged or tender. No suprapubic tenderness or mass could be elicited. The external genitalia appeared normal. Rectal examination was negative. The voided urine was grossly bloody. The patient was admitted to the hospital for urologic investigation. His red blood count was 4,060,000; white blood count 5,600 with a normal differential count; hemoglobin 82 per cent; nonprotein nitrogen 32 mg./per cent. Bleeding time 2 minutes, clotting time 2½ minutes. The Hinton test was negative. Urinalysis showed specific gravity of 1.025, acid reaction, 0 glucose, 0 acetone, 0 to 2 plus albumin and sediment loaded with red blood cells. The sedimentation rate was 6 mm. in 1 hour.

X-ray examination of the chest was negative. Excretory urography showed both kidneys and ureters normal.

Cystoscopy was performed February 12 under ether anesthesia. The bladder urine was grossly bloody. A tumor could be seen arising from the posterior wall of the bladder by means of a thin pedicle. A large blood clot was superimposed over the tumor mass. The trigone and both ureteral orifices appeared normal. The tumor had a cystoscopic appearance of a small bunch of grapes. A tentative diagnosis of sarcoma of the urinary bladder was made and surgical exploration advised.

Suprapubic exploration of the urinary bladder was done. A tumor mass was seen having a long, thin pedicle arising from the posterior wall of the bladder, behind the trigone. It consisted of many small cystic excrescences. A wide segmental resection was carried out, and a suprapubic cystostomy performed. Postoperative recovery was smooth.

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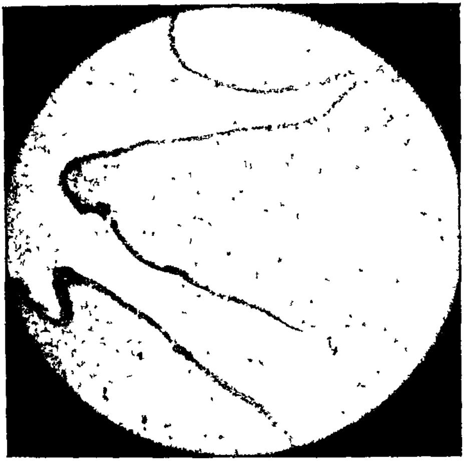

Fig. 1. Phot [illegible] of surgical specimen removed from bladder of 7-year-old child [illegible] fibrous polyp. Note regular, undisturbed, single layer of transi- [illegible] underlying edema of submucosal tissue. Section taken through one of many cystic excrescences, which gave tumor gross appearance of small bunch of grapes. No evidence of malignancy.

The surgical specimen was examined by Dr. Leslie S. Jolliffe, pathologist. The tumor measured 1.6 by 1.3 by 1.3 cm. It was attached by a very thin pedicle to the central point of an oval fragment of the bladder wall measuring 3.5 by 3.0 cm. and having a thickness of 1.5 cm. It had a rubbery-like contour composed of ovoid fronds with a grey, semitranslucent appearance. Microscopically (fig. 1) the tissue was composed of pedunculated outgrowths of connective tissue having an edematous stroma. The epithelium was transitional in type and was layered over the several polypoid excrescences. No epithelial anaplasia or invasion was seen. A few acidophilic intraepithelial inclusions were present. There was no evidence of malignancy. Diagnosis: Benign polyp of the urinary bladder.

Follow-up studies included cystoscopic examination in November 1947 (twenty months postoperatively). This revealed a healthy bladder with no evidence of tumor. Physical examination June 14, 1952 (six years, 3 months postoperatively) revealed a healthy boy of 13 with a negative physical examination. The urinalysis was negative for cellular elements, albumin, and glucose.

DISCUSSION

The case reports collected from the literature are summarized in table 1. It can be seen that in addition to the 9 cases of benign tumors reported in the literature by Deming in 1924, twenty additional cases have been found. This makes the total number of benign tumors, including the case reported herein, to be thirty. It appears that there is a marked preponderance of this disease in male patients as compared to the female, the ratio being 21 males to 9 females. The majority, 83 per cent, occurred before the age of 7 years and in half of the

TABLE 1. *Benign tumors of urinary bladder in childhood: Summary of cases collected from literature*

Case Number	Author	Year Reported	Sex	Age	Type of Tumor	Operation	Follow up
9 cases collected by Deming in 1924							
1	Bryant	1886	F	3	Fibromyoma	Removed by sound	Cured—6 yr. follow-up
2	Crik	1889	M	5	Fibroma	—	Died
3	Forster	1860	M	2	Fibromyoma	Removed by sound	Died
4	Frisch	1894	F	9	Fibroma	Suprapubic	Cured
5	Huesler	1905	M	1½	Fibroma	None	Died
6	Kaufman	—	M	2	Myoma	None	Died
7	Koll	1911	M	13 mos.	Polyp	Suprapubic	Cured
8	Martini	1874	M	New-born	Dermoid cyst	Suprapubic	Died 10 days postop.
9	Robitchek	1914	M	4½	Telangiectasis, fibrous polyp	Suprapubic	Cured
5 cases of hemangioma collected by Macalpine in 1930							
10	Macalpine	1930	M	14	Cavernous hemangioma	Segmental resection	Cured
11	Berliner	1902	F	11	Hemangioma	Suprapubic fulguration	Controlled bleeding for ? time
12	Hubner	1923	F	11	Angioma	Segmental resection followed by TUR	Improved
13	Scholl	1922	F	7	Cavernous angioma	No operation	Died
14	Arbuthnot Lane	1895	M	3½	Hemangioma	Suprapubic cystotomy	No follow-up

Case reports collected since 1924

15	White	1931	F	7	Fibromyoma	Suprapubic excision	Cured
16	Kiss	1932	M	7	Neurofibroma	No operation	Died
17	Rathbun	1937	M	2	Hemangioma	Suprapubic excision	"Recovered." No follow up
18	Ridlon	1939	M	3	Fibropapilloma	Suprapubic excision	Cured—2½ yr follow up
19	Bongiorno	1940	M	2	Fibromyxoma	None	Died
20	Chalkeley and Bruce	1942	M	9	Neurofibroma	Suprapubic	No follow up
21	Meade	1943	M	5	Benign myxoma	Suprapubic excision	Cured
22	Kapur	1944	M	$1\frac{2}{3}$	Capillary hemangioma	Trans excision	No follow up
23	Sansone and Galleto	1948	F	4	Leiomyomatous fibromyxoma	Suprapubic excision	Died
24	Ammaniti	1949	M	$1\frac{1}{3}$	Polyp	Suprapubic excision	Cured—2½ yr follow up
25	Pitts	1949	M	7	Neurofibroma	Sup biopsy, skin ureterostomy, x ray treatment	Persistent disease
26	Boden	1950	M	2½	Polyp	Suprapubic excision	Recovery
27	Higgins, Williams and Nash	1951	F	6	Hemangioma	Suprapubic fulguration	Recovery
28	Higgins, Williams and Nash	1951	M	"Small boy"	Multiple wart like naevi	TUR followed by suprapubic resection	Recovery
29	Higgins, Williams and Nash	1951	F	1 mo	Neurofibroma	Suprapubic cystostomy	Died 7th postop day
30	Ganem and Ainsworth	1955	M	7	Polyp	Segmental resection	Cured—6 yr follow up

patients the disease occurred before the fourth year of life. Pathologic reports in these cases are as follows:

Hemangioma	9	Fibromyxoma	2
Polyp	5	Fibropapilloma	1
Neurofibroma	4	Benign myxoma	1
Fibroma	3	Myoma	1
Fibromyoma	3	Dermoid cyst	1

Regarding the pathology of these tumors, there is considerable lack of knowledge. Targett in 1896 stated that all polypoid growths which are attached to the mucous coat of the bladder and which are variously described as mucous polyps, fibrosarcoma, fibromyxoma, and myxosarcoma and the like, should be described as sarcoma. R. F. O'Neil in 1915 stated that the vast majority of bladder tumors in the young are polypoid, rounded elevations of mucous membrane with a constricted base or pedicle. Whereas microscopically the proportion of fibrous and cellular or other elements may vary, nevertheless, pathologically, they are considered under one group since clinically they certainly have one point in common, being almost uniformly fatal. Ridlon as recently as 1939 stated that when a diagnosis of bladder tumor is made in a child, he believes that it should be considered malignant.

The relationship between benign and malignant tumors is not clear. It is thought by Martelli that malignant degeneration of a benign tumor is possible. Colston has suggested that the pedunculated type of bladder sarcoma may develop by malignant degeneration of a benign fibromyxoma. Herbut states, however, that malignant transformation of benign tumors has not been recorded. As for fibromyxoma, Shatz considered that this tumor may be a transition type between the villous polyp, which is benign, and the myxoma, which is very malignant. Deming considered the fibromyxoma "relatively benign." It is more slowly growing, has a long thin pedicle and is often located on the posterior wall of the urinary bladder. Surra Canard also considers fibromyxomas benign.

One can not escape the conviction that there is much confusion in the pathologic classification and description of myxomatous tumors. Herbut states that most myxomatous tumors of the bladder probably represent edematous fibromas and since both elements are usually demonstrable, they may be properly designated as fibromyxoma. The illustration in his text book (fig. 119, p. 257, vol. 1) appears identical histologically with the case reported here. One frequently reads descriptions of bladder tumors in childhood in which the tumor is likened to a "bunch of grapes." This can be misleading because this description is given by Deming to sarcomas. But after cystoscopic visualization of the tumor in the case just reported, we were able to apply this same description to the lesion found in our patient, a benign polyp. This is consistent with the observation of Cecil that the gross appearance of bladder sarcoma is not characteristic enough to distinguish it from other tumors. It would seem therefore, that the only safe way to determine the true nature of the tumor is by microscopic examination of the tissue removed by transurethral or suprapubic biopsy.

It would also seem unreasonable to consider all bladder tumors in childhood as malignant or potentially malignant. Every effort should be made to differentiate a malignant from a benign tumor and treatment rendered accordingly. The prognosis of malignant tumors thus far has been grave. In Ammaniti's series of 151 cases of bladder tumors in childhood he could find not a single unequivocal instance of definite cure in a child. A possible exception may be the case reported by Dick and Flint of leiomyosarcoma treated by segmental resection with a 3½ year follow-up, at which time cystoscopic examination showed no evidence of tumor recurrence. This one possible exception does not vitiate the clinical observation that the mortality of malignant tumors in the past has closely approximated 100 per cent.

SYMPTOMATOLOGY

The early sign of bladder tumor in the adult is hematuria, but in children hematuria as the presenting sign is less common except in hemangioma of the bladder. Usually there is disturbance in the functional state of the bladder causing persistent enuresis, dysuria, pain on micturition, suprapubic or perineal pain. At times acute urinary retention may develop. Frequently, there is secondary urinary infection causing severe burning and frequency with systemic evidence of pyelonephritis. Finally, because of their predilection for the trigone and base of the urinary bladder, these tumors usually cause ureteral obstruction with the symptoms and signs of renal insufficiency. If the mucosa becomes ulcerated, then hematuria occurs, sometimes causing frank hemorrhage with secondary anemia. Rarely the tumor may protrude through the urethra and present externally at the urethral meatus. Finally, there is associated anorexia with disturbance in the nutritional state.

DIAGNOSIS

Accurate diagnosis implies a high index and low threshold of suspicion for this condition. In any enuretic with a palpable suprapubic mass with or without hematuria, one must rule out bladder tumor. In any child with disturbed bladder habit, one must rule out bladder tumor. Finally painless hematuria, as in our case, calls for complete urologic study in order to identify the source of the bleeding. If angiomas are demonstrable on the skin, then a bladder hemangioma must be considered.

At least excretory urograms should be ordered. If the upper urinary tracts are normal, then cystoscopy becomes imperative. A negative cystogram shadow observed during the course of excretory urography is obviously not adequate exclusion of bladder disease. Our patient had a large, pedunculated tumor, and yet review of the bladder shadow even in retrospect failed to reveal the presence of any abnormality. If a tumor is identified, it is desirable to perform transurethral biopsy if this is possible. Aspiration suction biopsy has been suggested and at times it may be possible, in this way, to obtain tissue sufficient for diagnosis. Whether exfoliative cytology will prove to be of help is unknown since no report of its use in the diagnosis of bladder tumor in children has been reported. It is possible that in the pedunculated tumors some cells may be shed into the voided urine and help to identify the nature of the tumor. At times one will have to depend on surgical exploration of the bladder with biopsy to determine whether the tumor is benign, in which case conservative surgery of the blader is indicated, or whether it is malignant and calls for radical surgical intervention.

TREATMENT

The most fundamental principle to be applied to the treatment is the early recognition of this disease. In benign cases this would imply clinical recognition of the disease before the upper urinary tracts are damaged by back pressure and superimposed urosepsis. With our modern chemotherapy and antibiotics renal infection can be better controlled and the upper urinary tracts can be better preserved once the obstructing tumor has been removed. In benign cases the surgical treatment is conservative surgery consisting of suprapubic excision with or without fulguration of the bladder base and radon seed implantation or segmental bladder resection as was performed in our case.

CONCLUSION

Bladder tumors in children, though rare, impose a very serious threat to the life of the individual harboring the growth. Even benign tumors have in the past carried a 50 per cent mortality rate. The mortality rate of malignant tumors closely approaches 100 per cent. The only hope of improving this grave prognosis lies in the early detection of these tumors. This must come about by the more frequent application of modern diagnostic procedures to pediatric patients having disturbed bladder habit with or without hematuria or pyuria. In this way early diagnosis would lead to proper surgical management before irreversible changes in the upper urinary tracts have taken place and before the lesion has grown beyond the confines of surgical resectability. A satisfactory histologic diagnosis is essential to proper surgical management and accurate prognosis.

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HUMAN BLADDER NEOPLASTIC CELLS IN TISSUE CULTURE

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The finding of a number of urethral recurrences of papillary bladder tumors aroused our interest in the properties of free bladder tumor cells, particularly their viability The culture of bladder tumors is not a new subject, although there has been a recent revival of interest since the reports of Dr R G Bunge and co-workers[1] [2] [3]

There are many interesting questions, the answers to which might be sought by tissue culture methods The question of the viability of sloughed cells is one Another is whether diagnosis by exfoliated cells could be made more accurate by culture One might hope to learn what simple method would best destroy viability in free cells Of more remote interest are theoretical questions as to the possibility of influencing the growth of bladder tumor cells by artificial means such as use of hormones or other substances in the culture medium

Unfortunately only a small portion of this program was realized before the project had to be terminated It was thought best to report the results so far obtained

Tissue culture studies reported in this paper were concerned with two problems 1) Are the cells sloughed from the urinary bladder containing papillary tumor still alive and capable, therefore, of reimplantation within the urinary tract? 2) What are the optimum conditions for growth of bladder papillary tumor cells *in vitro* and what morphological cell types are found in such growing cultures?

MATERIALS AND METHODS

A Sedimented urine cells Urine was obtained by catheterization from normal control patients and patients with diagnosed malignancy, regardless of sex, and centrifuged at low speed The supernate was discarded and one drop of the cell suspension was mixed with two drops of a mixture of rooster plasma (for clot formation), chick embryo extract, human cord serum, 500 units per ml of penicillin and 250 micrograms of streptomycin The cells were prepared on circular coverslips for stationary double coverslip cultures or on 7 by 16 mm slips for insertion into rotating Porter roller flasks All cultures were kept at 35°C The feeding solution contained embryo extract, serum and Tyrode solution, and was changed twice each week A large series of stationary and roller cultures was set up with each specimen Urine cultures used for special cytological study were mounted in a thin plasma clot on single No 1 thickness 40 by 40 mm glass squares and inverted over special phase contrast slides

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Read at annual meeting, North Central Section of American Urological Association Detroit, Mich October 8, 1954

* Present address Cancer Research Foundation, Harlem Hospital, New York, N Y

[1] Bunge R G and Kraushaar, O F J Urol , 63 473 475, 1950

[2] Bunge R G and Stein, R J J Urol , 64 646, 1950

[3] Bunge R G J Urol , 67 740, 1952

Viability of urine cells was determined by four methods:

1) Prolonged direct phase contrast microscopic observations.

2) Aqueous eosin test for living cells (living cells are unstained, dead cells stain pink within two minutes).

3) Time lapse cinematographic observations over extended time intervals. These studies were made using the 16 mm. Paillard Bolex movie camera attached to a Rolab electronic timer device.

4) Observations of clot lysis, migration of cells and mitotic divisions in cultures.

B. Bladder papillary tumor tissue. This tissue was obtained from surgery after aseptic removal by electrosurgery and cultured within two hours using the procedure and media described above. One mm.^{3} fragments were used. One specimen was stored in the feeding solution at 4°C for 5 days before culturing. Excellent growth followed.

RESULTS

A. Sedimented urine cells. Cells of four normal patients and 14 patients with diagnosed malignancy were studied. Normal urine cell suspensions prepared in a plasma clot had cell populations of only one to two cells per low power field in contrast to bladder tumor suspensions which had 50 to 100 cells per low power field. The transitional type tumor cell and its rounded type were most numerous. An occasional squamous cell, a few granular leukocytes, lymphocytes and erythrocytes were present. Intense cytoplasmic activity was observed in fresh

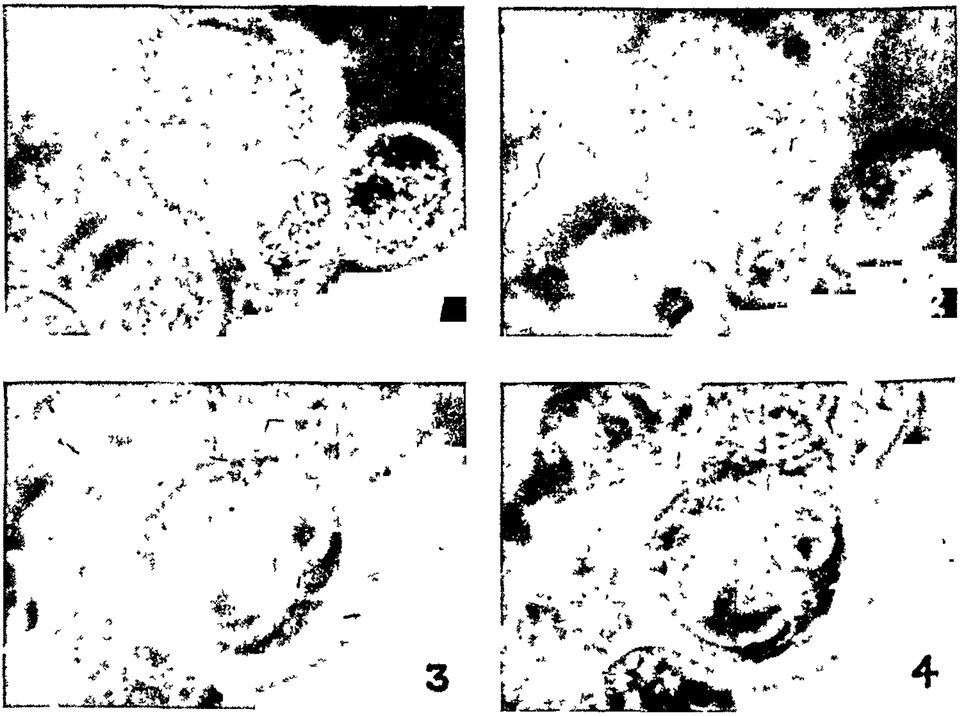

FIG. 1. Scenes of tumor cell in tissue culture undergoing amitotic division. Reproduced from time lapse photomicrographic movie strip

smears of cells and in 48 hour cultures. Such cytoplasmic movement ceased in older cultures although cells remained extended and in excellent morphological condition. These cells always formed surface liquefaction pools, indicative of cell lytic activity.

Eosin counts indicated that less than 5 per cent of the cells were dead in fresh smears and in 48 hour cultures. Additional evidence of activity was observed in

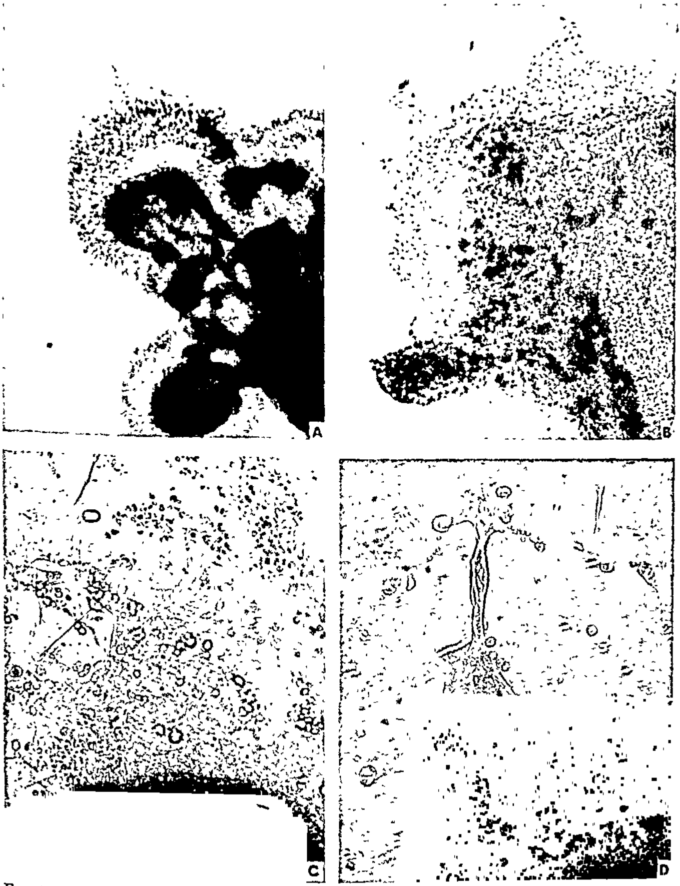

FIG. 2. *A* and *B*, case F. B. *A*, polyp in freshly prepared plasma clot culture. *B*, 24-hour growth from polyp. Jenner-Giemsa stain. *C*, 48-hour living culture showing cytoplasmic bridges. *D*, 4-day outgrowth showing band of epithelial cells. Unstained.

single frame photomicrographs taken every 10 seconds and then speeded up. Successive changes in a tumor cell are seen in figure 1. The cell is undergoing amitotic division. Such a form of division is of particular interest in a tumor cell.

B. Bladder papillary tumor tissue cultures. Cultures from biopsies of thirteen papillary tumors and one renal tumor (adenocarcinoma) grew better in stationary slide cultures than in rotating roller flasks. A freshly prepared papillary process in tissue culture often resembled the same structure in situ (fig. 2, *A*). The transitional cells at the surface are loosely attached. Twenty-four-hour outgrowth from such a papillary process is seen in figure 2, *B*.

Extensive epithelial sheet outgrowth, with no fibroblasts, occurred in 70 per cent of the fragments. Fibroblastic growth alone was found in 10 per cent of the cultures. Liquefaction within 24 hours was a consistent finding in all stationary cultures with or without epithelial outgrowth. Cultures in roller tubes lysed the clot and slipped off the glass before sheets of cells could adhere to the glass.

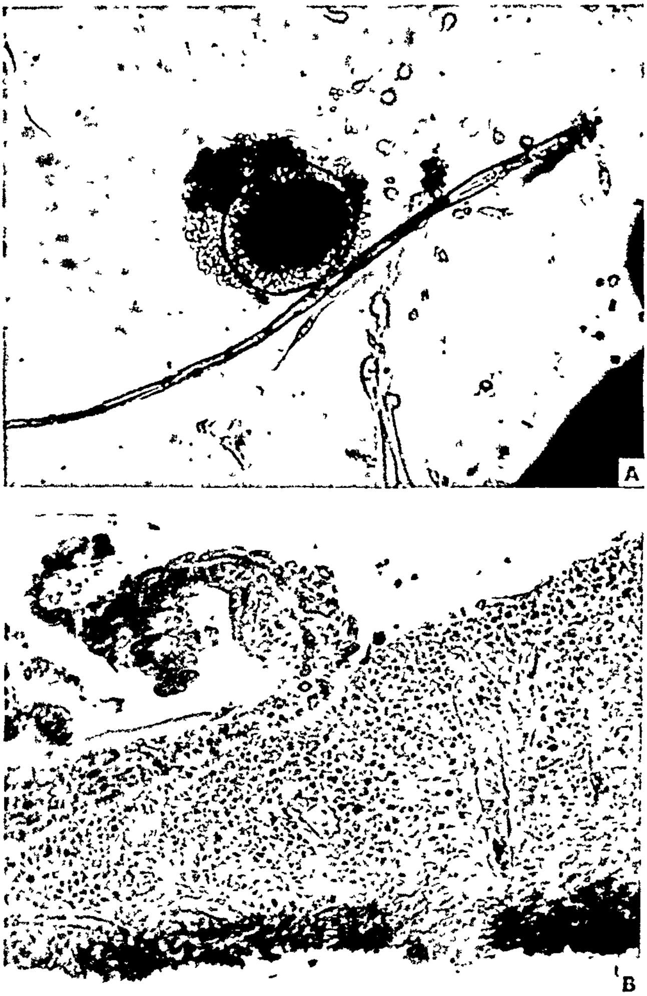

FIG. 3. Case J. L. *A*, living culture with detached epithelial cells in ball formation; 24-hour culture. *B*, 7-week tissue culture cross section. Note cellular disintegration except for plasma cells. Capillary structure remained apparent. Jenner-Giemsa stain.

Earliest cell migration was of granular leukocytes Epithelial sheets appeared as early as 18 hours, growing rapidly as a single cell sheet These sheets continued to grow up to 7 days, lysing the plasma clot and forming intercellular bridges characteristic of epithelial cells (fig 2, *C*) The nucleus occupied more than one third of the cell and nucleoli were prominent Cytoplasmic granules were minimal and a few mitochondria were located near the nucleus

Uneven tensions at the edge of sheets of cells caused advancing sheets to form stretched narrow bands of cells (fig 2, *D*) Frequent patching with plasma was needed to anchor the sheet, due to rapid lysis

Intact solid sheets of cells rarely persisted beyond two weeks Older cultures when transferred to new clots formed liquefaction pools only Disintegration of cell sheets began with vacuolization of individual cells with subsequent cytolysis Large liquefaction pools formed within the sheet after seven or more days, leaving islets of epithelial cells

An adenocarcinoma of the kidney biopsy and one papillary tumor, biopsied at two different times, produced a dense outgrowth of fibroblasts with few epithelial cells and no liquefaction.

Of interest was a papillary tumor (case J L) in culture which formed a liquefaction pool but produced no outgrowth Papillary structure was maintained in roller tubes for 7 weeks Only one group of cells became detached and formed a ball of clear cells (fig 3, *A*) Serial sections of the explant after 7 weeks showed that all cells were dead except the plasma cells which stained brilliantly Blood vessel structure persisted and on the glass surface were densely basophilic macrophages, filled presumably with hemosiderin (fig 3, *B*)

DISCUSSION

Evidence has been presented to indicate that the urine cells present in the bladder of the patient with papillary tumor are viable cells and biologically capable of continued growth *in vivo* under certain conditions Cells of this type might be those partaking in reimplantation sites following specific bladder surgical procedures

The need of a physical substrate for epithelial sheet outgrowth seems apparent in an analysis of these data Although conditions in culture described in these experiments were not optimum for long-term, continuous culturing they point the way to future requirements

Fragment outgrowth of papillary tumors agreed with the early experimental findings of Burrows, Burns, and Suzuki[4] who noted clot lysis and epithelial sheet formation They reported that benign papillary tumors did not grow in tissue culture

Clot lyis ability, dependent on the presence of a profibrinolysin present in the plasma clot and a cell activator derived from the tumor cells, was a consistent finding in all cultures whether a sheet of cells grew out or not It was of interest to note that the papillary tumor epithelial sheets appeared within 24 hours in contrast to normal epithelial sheets, which usually do not appear before 48 to 72 hours[5]

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[4] Burrows M T Burns J E and Susuki Y J Urol 1 3-15 1917

[5] Cameron, G Tissue Culture Technique New York Academic Press Inc , 1950

SUMMARY

Sloughed bladder cells present in the urine showed definite cellular activity in tissue cultures under conditions good for growth of papillary tumors from the bladder.

Papillary tumor tissue formed liquefaction areas and clear, fast growing sheets of epithelial cells in stationary double coverslip cultures while similar fragments floated off the clot after liquefaction when in rotating Porter roller flasks. Clot lysis was a consistent finding in all cultures of tumor tissue whether epithelial cell outgrowth occurred or not. Frequent patching of cultures with plasma was needed to maintain healthy epithelial sheets.

The cytology and patterns of growth of the epithelial sheets were described in detail. Intact sheets persisted up to two weeks without signs of cellular vacuolization. Fibroblastic growth was absent.

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MANAGEMENT OF URETHRAL CARCINOMA IN THE FEMALE

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Carcinoma of the female urethra although uncommon is by no means rare McCrea[1] in an excellent review of the literature in 1952 listed 546 authenticated cases An additional nine were found in the literature but could not be verified

It is the purpose of this paper to add an additional 32 cases and discuss primarily the management of this disease Each of the 32 cases has been proven by histological section The series has been divided into three clinical groups as determined by the anatomical location of the primary lesion These are vulvo-urethral, which include those lesions that are primary in the urethra with extension to the vagina and vulva, urethral, which is limited to the urethra, and urethrovesical, which includes those lesions primary in the urethra with extension into the bladder

INCIDENCE

In New York State, exclusive of New York City, the incidence of this neoplasm is 0 21 per 100,000[2] Seng and Siminovitch[3] reported an incidence of 1:1,191 in female admissions at the Royal Victoria Hospital in Montreal, Quebec At our Institute, which is devoted entirely to the research and treatment of cancer, there were 32 cases in over 45,000 female admissions or an incidence of 1 1,500

Primary carcinoma of the urethra in the female occurs most frequently in women after the menopause The youngest patient in this series was 39 years and the oldest, 80 years The average age was 62 7 years This disease is most common in married women All of the patients were caucasian

PATHOLOGY

Of the 32 proven cases here reported, there were 28 squamous cell carcinomas (fig 1, *A*), two transitional cell carcinomas (fig 1, *B*) and two adenocarcinomas (fig 2)

Colby[4] states that the mucosa of the female urethra consists of stratified squamous epithelium that becomes transitional near the bladder

Ricci et al [5] in 1950 published a histologic study of the female urethra in which they noted that the normal paraurethral glands found near the external orifice occasionally are seen in the midportion of the urethra and rarely a few glands are found near the internal urethral orifice

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Read at annual meeting, Northeastern Section of American Urological Association, Chateau Frontenac, Quebec City, Quebec, Canada, September 19-22, 1954

[1] McCrea, L E Malignancy of the female urethra Urological Survey, 2 85-149, 1952

[2] Annual Average Cancer Incidence Rates, Female, by Age and Sites New York State Exclusive of New York City—1949-1950, New York State Department of Health

[3] Seng, M and Siminovitch, M Carcinoma of the urethra in the female Canad M A J, 58 29-33, 1948

[4] Colby, F H Essential Urology Baltimore Williams & Wilkins, 1953, 2nd ed, p 91

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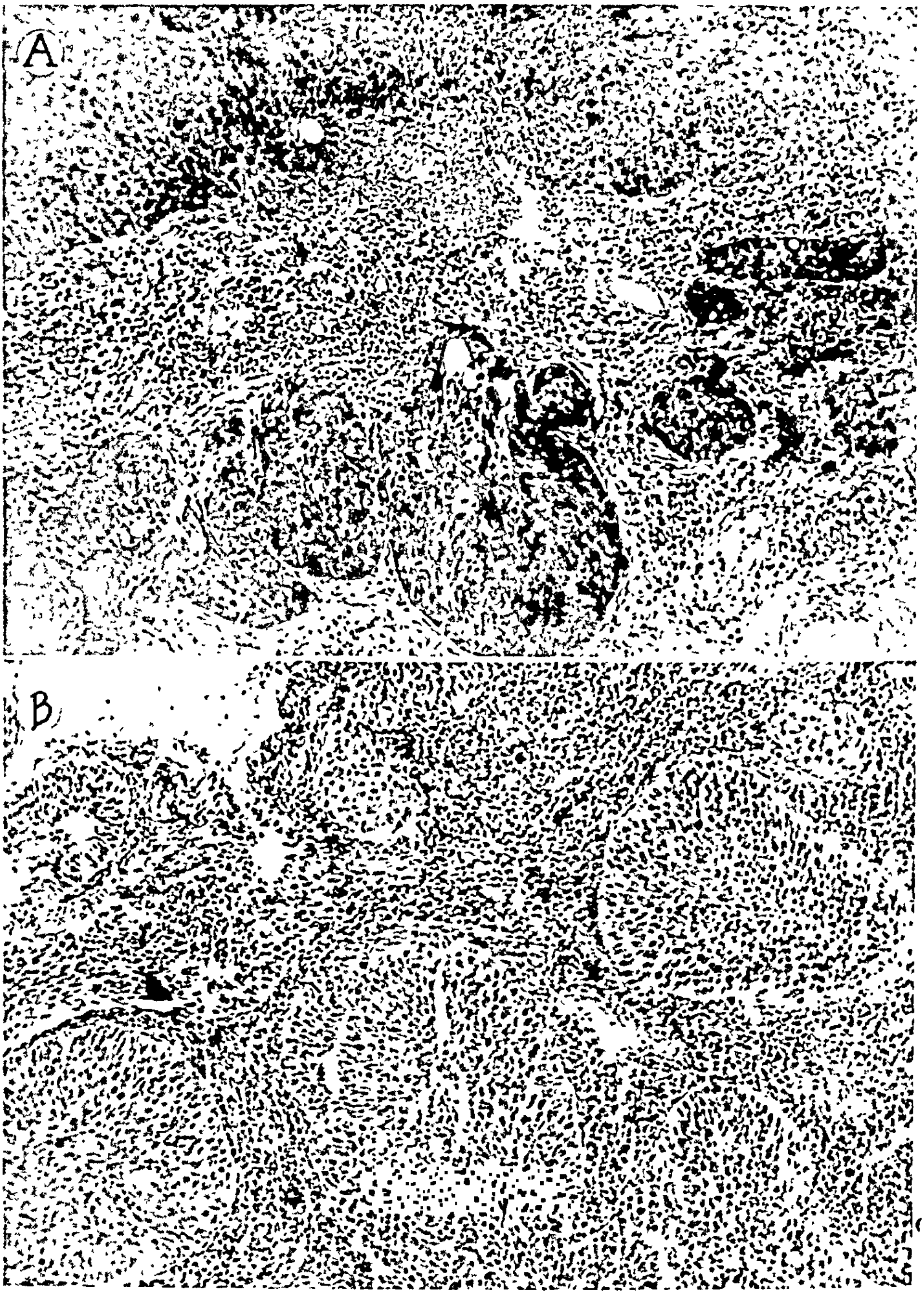

FIG. 1. *A*, squamous cell carcinoma of urethra. Tumor cells show differentiation and pearl formation. *B*, transitional cell carcinoma of urethra. Tumor cells are infiltrating in large plaques, showing typical transitional cell pattern.

The histological presence of the three types of carcinoma found in this series can be adequately explained on the basis of these studies.

All tumors were found to be invasive in character. Histologically, the tumors were classified according to Broders'[6] method. This method was suggested by

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[6] Broders, A. C.: Epithelioma of genito-urinary organs. Am. Surg., 75: 574–604, 1922.

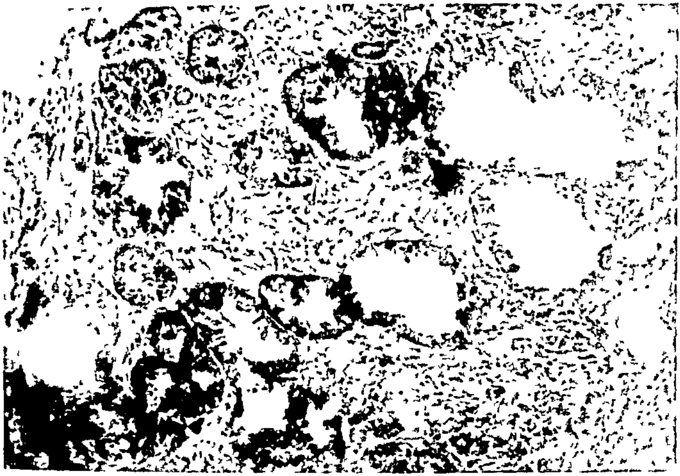

FIG. 2 Adenocarcinoma of urethra. Tumor cells are arranged in typical gland forming pattern showing adenocarcinoma

TABLE 1

	Group 1	Group 2	Group 3	Group 4
Squamous cell carcinoma	0	9	10	9
Transitional cell carcinoma	0	0	2	0
Adenocarcinoma	0	0	2	0
Total	0	9	14	9

Broders in which he divided the tumors into four groups corresponding to the degree of deviation of the tumor from normal epithelium. These urethral tumors, therefore, have been classed according to their cellular characteristics, rather than their invasive tendency.

Table 1 lists the number of tumors found in each of the four groups From this table, it can be readily seen that the majority of tumors, 14 or 43.7 per cent, are found in group 3, while 9 or 28.1 per cent are found each in group 2 and group 4. There were no group 1 tumors.

An attempt has been made to correlate the histological group of the tumor with the average survival of the patient. This is seen in table 2.

Table 2 demonstrates that one cannot correlate well the histologic pattern of the tumor with its malignant behavior.

ETIOLOGY

The etiology of carcinoma in the female urethra is not known. Several factors however, have been linked to the onset of this disease. Chronic inflammation and

TABLE 2

	Number of Cases	Average Survival (mos)
Group 1	0	0.
Group 2	9	38.6
Group 3	14	57.5
Group 4	9	57.3

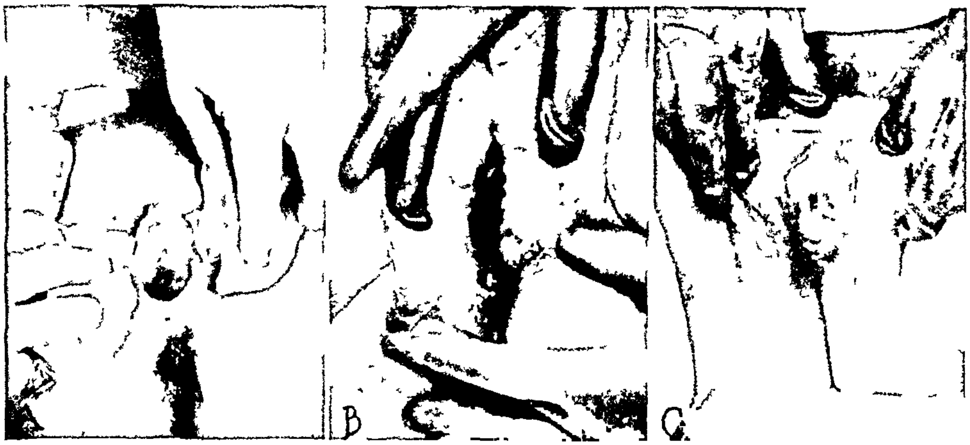

FIG. 3. *A*, urethral cancer. Note appearance of lesion with irregular surface. *B*, vulvo-urethral cancer Note involvement of labia from original urethral lesion. *C*, urethral caruncle. Note size, typical appearance with smooth red surface.

infection of the urethra, not an uncommon finding in middle-aged women, may be associated with urethral tumors. Childbirth injuries may play a part in the onset of carcinoma of the urethra.

The role played by urethral caruncle in causing carcinoma of the urethra is still not clear. In this series, 5 cases had urethral caruncles removed prior to the onset of their carcinoma. In two of the cases, the presenting lesion looked grossly like a caruncle. Biopsy, however, showed the coexistence of carcinoma and caruncle.

DIAGNOSIS

In establishing the diagnosis of carcinoma of the urethra, two other urethral disorders must be differentiated: 1) urethral caruncle and 2) urethral prolapse.

A typical carcinoma (fig. 3, *A*) is an irregular, granular, easily bleeding mass protruding from the urethral orifice. However, urethral carcinomas vary greatly in size and appearance (fig. 3, *B*). A very early tumor might appear as a small rounded elevation under the meatal lip.

Caruncles (fig. 3, *C*) are most commonly seen on the posterior lip of the urethral meatus. They are usually smooth, red, tender and not indurated. They are often less than 1 cm. in diameter.

Caruncles which show a disruption of the orderly transitional pattern and minor degree of cellular atypia may be confused with cancer.

Urethral prolapse is usually symptomless and rarely bleeds. It is continuous with the urethral mucosa, soft, and nontender.

Clinical diagnosis alone carried a considerable percentage of error For this reason, any lesion of the urethra must be biopsied for certain diagnosis

SYMPTOMATOLOGY

Bleeding is the principal symptom of urethral carcinoma in the female This may be bleeding associated with urination (hematuria) or bleeding from urethral or vaginal surfaces Twenty-six cases (81 2 per cent) had bleeding when first seen Seventeen cases (53 1 per cent) had urethrovaginal bleeding and 8 cases (25 per cent) had true hematuria One case had both forms of bleeding No correlation between the site of the lesion and the type of bleeding could be made from this study Ulceration of superficial lesions accounted for bleeding in 11 cases (43 5 per cent) Another salient feature associated with bleeding was the presence of a foul vaginal discharge which was usually watery in consistency and serosanguinous in appearance

Frequency of urination occurred in 14 cases (43 7 per cent) and was most frequently associated with burning on urination Urgency was not a prominent symptom, appearing in only 2 cases Some of these women (8 cases or 25 per cent) complained of painful urination Three cases were incontinent and 2 women required suprapubic drainage due to complete obstruction

In only 1 case was the disease heralded by metastatic phenomena In this case, the chief complaint was one of shoulder pain of 3 months' duration X-ray revealed metastases to the entire right shoulder girdle

The average length of symptomatology prior to diagnosis was approximately 1 year (12 2 months)

METASTASES

Metastatic phenomena in carcinoma of the female urethra are not uncommon J S Eisenstaedt[7] states that one-third of the cases present enlarged inguinal nodes at the time of admission Riches and Cullen[8] in their excellent review of the subject even made the suggestion that, "Metastases in inguinal glands are sufficiently common (50 per cent) to warrant a full consideration of their treatment either by removal or irradiation in all cases "

Fifteen (47 per cent) of our 32 cases had enlarged inguinal nodes when first seen Two of these were proven by biopsy Inguinal node enlargement was seen in 7 cases (22 per cent) classed as urethral, 5 cases (15 5 per cent) classed as vulvo urethral and 3 cases (10 per cent) classed as urethrovesical

Gray[9] outlined the route of metastases when he stated that, "Lymphatic vessels are numerous in the submucosa and drain into the inguinal nodes from the distal portion and into the deep pelvic nodes from the proximal portion of the urethra These latter are the external and internal iliac nodes and the hypogastric nodes and sometimes drain into the node at the promontory of the sacrum "

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[7] Eisenstaedt, J S Primary carcinoma of the female urethra with metastasis Am J Surg , **81** 612-617, 1951

[8] Riches, E W and Cullen, T H Carcinoma of the urethra Brit J Urol , **23**· 209, 1951

[9] Gray, J H The relation of lymphatic vessels to the spread of cancer Brit J Surg , **26** 462, 1939

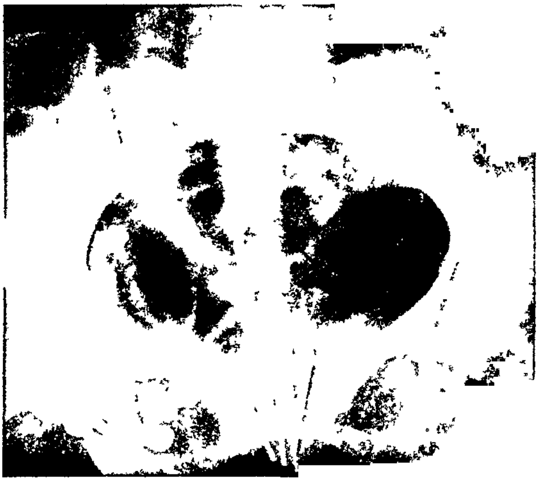

FIG. 4. Showing radium needles in situ.

Gilchrist[10] concludes that the lymphatic spread of the carcinoma is primarily embolic and that the nodes where the emboli lodge prevent further spread until the node is overwhelmed by carcinoma.

Clinically distant metastases were found in only one case. However, the autopsy material showed widespread metastases along the route outlined by Gray.

TREATMENT

Treatment of carcinoma of the female urethra has varied considerably in the past. During the last 20 years, radiation has replaced extensive surgery. Many cases are originally treated by surgical biopsy and electrocoagulation. This is usually followed by irradiation. In this series, only 3 cases were treated by surgery and all of these cases received additional radiation. The remaining 29 cases were treated by some form of radiation therapy alone. On reviewing the records of the patients treated, it has been apparent that the radiation failures have been due mainly to the erroneous estimation of the true tumor extension and the inadequate irradiation techniques employed. With the methods that have been utilized, the best results have been obtained by interstitial irradiation.

Interstitial irradiation (fig. 4) is considered the treatment of choice for most localized urethral cancers. Cancers which are so large as to require an implant longer than 4 cm. should be treated by some other method. Low intensity radiation sources are the best and removable implants (radium element needles) are better than permanent implants (radon seeds) especially for the larger lesions. The minimal tumor dose employed with interstitial irradiation should be 4,500–5,000 gamma r within 4 days or 6,000 r within 6 to 7 days. Some urethral cancers, for example, the vulvourethral type, might be treated by vaginal radium element applicators comparable to those used in the treatment of primary vaginal cancer. However, this method is not too successful. For the treatment of vulvar lesions, the minimal tumor dose should be 6,000 gamma r within 5 to 7 days. In the past, x-ray alone has not been very successful. However, there are some extensive cancers where it must be employed in order to deliver suitable dosage to large volumes of tissue It is sometimes indicated following surgery because of possible residual cancer or definite recurrences in the operative site Occasionally a judicious application of radiation will decrease the size of the cancer or its metastases so that some degree of comfort is afforded to the patient However, it should be noted that external irradiation is not very efficacious for the treatment of lymphnode metastasis The tumor dose should be from 5,000–6,000 r within 2 to 4 weeks depending upon the volume and the quality When lesions are so extensive that a combination of irradiation modalities is indicated, external x-ray and interstitial irradiation are sometimes employed The very nature of such an extent augurs against good end results Palliation, however, is sometimes obtainable for a limited period of time

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[10] Gilchrist, R. K : Quoted by Eisenstaedt, p. 614. Am. J. Surg., **81:** 612–617, 1951.

COMPLICATIONS OF RADIATION THERAPY AND THEIR TREATMENT

Whenever cancerocidal irradiation is given, certain complications arise The most noticeable one is in the reaction of the skin and mucous membrane This is very often disagreeable especially about the vulva This reaction may vary from a deep erythema to a moist desquamation The irradiated area should be kept as clean and as dry as possible Friction from motion or clothing should be minimized For a milder reaction, a 1 per cent aqueous solution of gentian violet may be painted on or sprayed upon the skin twice each day Should the reaction be of a second degree such as is common in the vulvar folds and groins, at the end or shortly after the end of radiation regimen, wet dressings of 2 per cent boric acid solution may be applied for several hours each day If the patient can tolerate a local anesthetic, the lanolin may be mixed with 1 per cent nupercaine or other local anesthetic ingredient It is often necessary to keep the patient in bed with a heated cradle over the pelvis To minimize secondary infection, antibacterial applications such as neosporin or polysporin ointment may be indicated General health measures should be accentuated This would include supportive treatment such as high protein diet, blood transfusion and parenteral fluids when indicated Roentgen sickness when not controlled by acceptable alteration of treatment technique may be ameliorated by mild sedation or by such pharmaceutical products as pyridoxin, dramamine, thorazine, etc Vesical tenesmus may sometimes be relieved by rectal suppositories of opium and belladonna Diarrhea when not controlled by bulk producers like metamucil, should be treated by suitable opiates The late sequelae are edema of the vulva, atrophy and telangiectasia of the skin and mucous membranes and subcutaneous fibrosis Such altered tissue is prone to inflammatory breakdowns following trauma and infection Vesicovaginal fistulas are rare and usually are due to the cancer itself

END RESULTS

Of the 32 patients who were examined up to 5 years ago, five received treatment elsewhere Of these five, one survived 5 years

The cases treated at the Roswell Park Memorial Institute and the methods of treatment are seen in table 3 The small number of patients in each category makes the result and percentage cures and failures statistically insignificant It is

TABLE 3. *Five year end results, cancer of female urethra, Roswell Park Memorial Institute 1931–1949*

Type of Radiation	Number of Cases	Died of Cancer	Lived over Five Years		
			With cancer	Without cancer	
				Number	Percentage
X-ray	6	6 AAAACB			
Radium needles	3	2 A A		1 A	33.3
Radon seeds	6	3 AAA		3 AAA	50.0
Teleradium	1	1 B			
X-ray and radium needles	1	1 A			
X-ray and radon seeds	8	4 AAAC	1 A	3 AAB	37.5
X-ray, radon seeds radium applicator	2	1 A		1 A	50.0
No treatment at RPMI: treated elsewhere	5	4		1	
TOTAL					
Examined	32	22		9	28.1
Treated	27	18	1	8	29.6

Code
A—Vulvo-urethral
B—Urethral
C—Urethrovesical

apparent, however, that interstitial irradiation was more successful than x-ray alone. This is mainly due to the fact that those cancers which received interstitial irradiation were more local in their extent than the cases treated by x-ray which were more advanced and treated with tumor doses woefully inadequate according to our present standards. The absolute 5-year cure rate for the entire 32 patients examined was 28.1 per cent. The relative 5-year cure rate for the 27 patients actually treated at this Institute was 29.6 per cent. The relative survival rate of the treated cases was 33.3 per cent. Nine of these latter cases has interstitial irradiation only and four of these lived 5 years without evidence of cancer or a 5-year cure rate of 44.4 per cent in these 9 cases.

The foregoing figures indicate that therapy of urethral carcinoma in the past leaves much to be desired. This is particularly true of the more advanced lesions, especially those of the posterior urethra with bladder neck involvement. Interstitial irradiation in the form of removable implants gave the best results in anterior and meatal carcinomas. The authors during the past 3 years have used radical surgery in the form of radical cystectomy and urethrectomy for the advanced urethral and urethral-vesical lesions. The follow-up periods to date have been too short to draw any definite conclusions, but the response of several of the patients to radical surgery has been encouraging.

CONCLUSIONS

A study of 32 cases of carcinoma of the female urethra is reported.

It is a condition encountered most frequently after 50 years of age.

Eighty-five of the cases were squamous cell carcinomas.

The importance of biopsy is emphasized, even though the lesions may have a benign appearance.

The symptoms vary greatly depending on the stage of the tumor but bleeding was the most common.

Metastases tend to develop early, the distal urethra to the inguinal nodes and the proximal urethra to the iliac nodes.

The best results have been obtained by interstitial irradiation.

The prognosis is serious.

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A CASE OF BALANITIS XEROTICA OBLITERANS WITH TELANGIECTASIS RESPONDING TO INTRAVENOUS PROCAINE

JOSEPH FARRINGTON, J. HAROLD NEWMAN AND ROBERT G. ROSSER, JR.

Balanitis xerotica obliterans is recognized as a chronic, progressive, sclerosing atrophic process of the glans and prepuce of the penis frequently leading to urethral stenosis (fig. 1, *B*). When the involvement of the glans is diffuse, it is white or ivory colored; if not diffuse, the admixture of white plaques and normal red tissue of the glans results in a mottled appearance. Another gross feature, first noted by Novy[1] and substantiated by the following case report, is the presence of telangiectases. These may also be noted microscopically (fig. 2).

Further observations are necessary to decide the relationship between balanitis xerotica obliterans, kraurosis penis, lichen sclerosus et atrophicus, scleroderma and leukoplakia. All these relationships are not within the scope of this report as they have already been adequately considered in the excellent studies of Freeman and Laymon.[2]

The treatment of well developed balanitis xerotica obliterans is difficult since the complete restitution of sclerotic parts to normal by any known means cannot be expected. In 1947, Farrington and Garvey advocated radical therapy by electrocoagulation to maintain an adequate urethral opening and to avoid the occasional cancerous degeneration.[3] The purpose of this report is to cite a typical case showing both objective and subjective response to intravenous procaine therapy. Almost identical results with two additional patients observed for 1½ years indicate a satisfactory treatment heretofore unreported.

CASE REPORT

E. C., a 62-year-old, white, married man and father of two grown sons, was first seen March 25, 1953. He stated that 1 year previously, he had first noted a sensation of "tightness" or tension in the penis associated with itching and burning on urination. Penile erections became increasingly painful, finally precluding coitus. The foreskin had always been moderately tight but could always be retracted. For the last 3 months, he had noted a thin, glairy, sometimes pink, discharge oozing from the edge of the foreskin.

Examination of the penis (fig. 1, *A*) disclosed moderate phimosis but the foreskin was freely movable over the corona. No adhesions were found but approximately 1.5 cm. from the dorsal border of the coronal sulcus a constricted sclerotic band could be palpated in the prepuce. The glans penis was hard and the surface parchment-like. Several white atrophic patches alternated with the softer red glans tissue. Overlying the right ventral sulcus and adjacent to the fren-

Accepted for publication September 22, 1954.

[1] Novy, F. G. Jr.: Balanitis xerotica obliterans. Arch. Dermat. & Syph., **43:** 397, 1941.

[2] Freeman, C. and Laymon, C. W.: Relationship of balanitis xerotica obliterans to lichen sclerosus et atrophicus. Arch. Dermat. & Syph., **49:** 57–59, 1944.

[3] Farrington, J. and Garvey, F. K.: Balanitis xerotica obliterans: Report of two cases. Urol. & Cutan. Rev., **51:** 96–97, 1947.

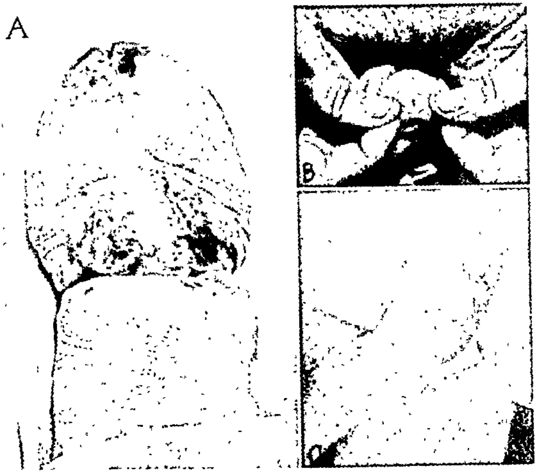

Fig. 1

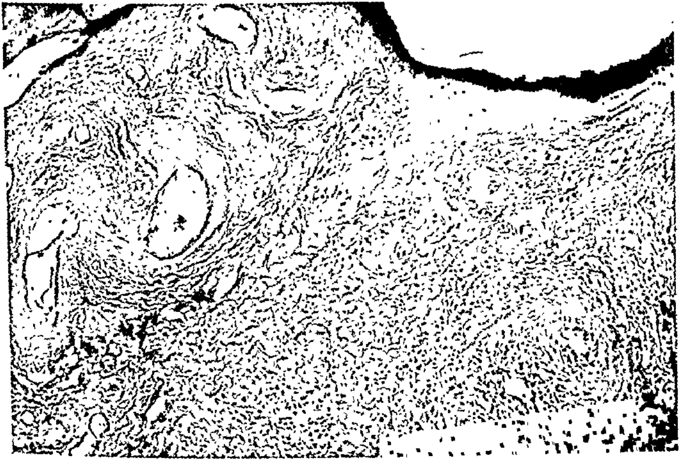

Fig. 2

ulum were two moist, atrophic, eroded patches, each measuring ¼ cm. in size. The frenulum itself was sclerosed and almost fibrotic. Numerous groups of superficial telangiectatic vessels coursed over the ventral surface of the sulcus and corona. The rest of the integument was normal and no lesions of lichen sclerosus et atrophicus could be found. Blood serology was negative; urinalysis was normal. A punch biopsy from the eroded patch on the sulcus and from a white atrophic, telangiectatic area adjacent to the external meatus near the frenulum showed the typical microscopic picture of balanitis xerotica obliterans. These histologic features were consistent with those seen in the fully developed condition (fig. 2). There was atrophy of the epidermis with relative and absolute hyperkeratosis as well as edema and homogenization of the papillary cutis. Perivascular inflammatory changes and diminution or loss of the elastic tissue were also seen. Perhaps the most striking histologic feature was a broad band of homogenization in the upper cutis.

He was hospitalized on April 6, 1953 for circumcision to relieve the phimosis. On learning there would be a waiting period of 5 days for the operating room, it was decided to institute therapy with intravenous procaine. This was done on the basis of a report,[4] and the unpublished experiences of one of us (J. F.) of favorable response of scleroderma to such treatment. Procaine therapy seemed rational as scleroderma and balanitis xerotica obliterans have certain similarities. The patient was given 500 cc of 0.1 per cent procaine in normal saline intravenously his first hospital day. Within 24 hours, he experienced marked relief from penile itching and paresthesia. He was given 1,000 cc of 0.1 per cent procaine in normal saline intravenously daily for the next 3 days. Circumcision was done on the fifth hospital day but preoperatively, marked decrease in the induration of the corona was noted. The surfaces which were formerly dry and fissured were smoother and unbroken. There was apparent decrease in the number and extent of the telangiectases. Microscopic examination of the excised foreskin showed a band of involvement typical of balanitis xerotica obliterans. This description, given independently by a second pathologist, was almost identical to the description of the first pathologist who examined the specimens from the corona. The patient was discharged from the hospital on April 16, 1953.

Follow-up examination after 3 weeks showed a well-healed operative scar of the circumcision. There was further diminution of telangiectases and in the induration of the corona. All the eroded patches and biopsy sites were completely healed and the patient was comfortable. At the end of 6 weeks, urination and penile erections were painless. Sexual intercourse was performed normally.

The patient was last seen November 27, 1954. He showed no evidence of recurrence of the disease, and had no discomfort or paresthesia. A photograph taken at that time is shown in figure 1, *C*.

SUMMARY

A typical case of balanitis xerotica obliterans of 1 year's duration in a 62 year old white man showed a favorable response to intravenous procaine therapy.

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[4] Turner, J. P. and Schmidt, F. R.: Treatment of scleroderma with procaine: Report of cases. J.A.M.A., 144: 1560–1561, 1950.

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ACCESSORY SPLEEN IN SCROTUM

JOHN E GLEN

Splenic tissue removed from the left scrotal compartment at operation, or discovered at autopsy is a rare entity. Such a case found at operation is of interest, and is here reported No attempt will be made to discuss the embryology involved

This condition should be considered in the differential diagnosis of lesion within the left side of the scrotum Emmett and Dreyfuss[1] reported a case found at operation, as did Andrews and Etter[2] Olken[3] presented a case found in autopsy Keizur[4] reported 2 cases in the *Journal of Urology*, and in a review of both foreign and domestic literature was able to find only eleven other cases of spleen within the scrotum The following is believed to be the fourteenth reported case

CASE REPORT

W A B, a 12 year old white boy, was referred to the office with a mass in the left scrotal sac which was first noted by the patient's mother at about seven years of age A pediatrician was told of this and advised that further investigation be done if the lesion became larger It was again noticed at the time of an appendectomy when the patient was 9 years of age Approximately three months before being seen, the patient acquired mumps Following this, the mass gradually increased in size with a dragging sensation and an occasional sharp pain being felt There were no urinary complaints and urinalysis was not remarkable

Upon examination, the right testicle, epididymis and cord showed nothing of note The penis was not remarkable A firm, nodular mass was found in the left scrotal compartment which measured approximately 5 by 3 by 2 cm and which appeared to involve the upper pole and body of the left epididymis The testicle did not feel remarkable and there was no enlargement of inguinal lymph nodes A diagnosis of multiple cysts of the left epididymis was made, and the patient was hospitalized

An exploration of the left scrotal compartment showed a firm, greyish-blue colored, nodular mass involving the left epididymis which measured approximately 3 by 2 by 2 cm This mass contained one spherical area, 8 mm in diameter attached to the superior portion The testicle did not appear remarkable There appeared to be no connection between the tumor mass and testicle, although they were closely adherent A routine epididymectomy was done, removing the tumor which was fixed to the head and body of the epididymis The blood supply of the tumor mass was easily seen and consisted of several dilated vessels which merged with the tumor These vessels bled easily on manipulation

The pathologic examination showed "Vas deferens—histologically normal, sperm not present" The tumor mass was reported as "Section shows very

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[1] Emmett, J M and Dreyfuss, M L Ann Surg, **117**. 754–759, 1943

[2] Andrews, S E and Etter, E F J Urol, **55**: 545–547, 1946

[3] Olken, H G Am J Path, **21**: 81–85, 1945

[4] Keizur, L W J Urol, **68**· 759–762, 1952

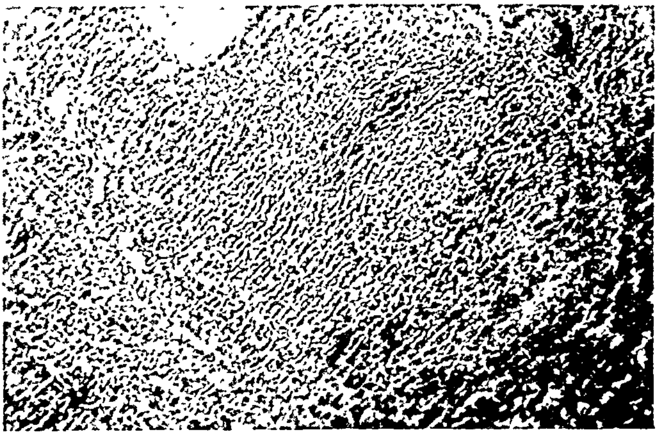

FIG. 1

characteristic splenic tissue with thick fibrous capsule, red pulp containing few red blood cells, distinct fibrous trabeculae and lymphoid nodules with characteristic central arteries. Many of the lymphoid structures have prominent germinal centers and lymphoblasts of normal appearance. Nowhere is there any evidence of abnormality or other type of tissue. Diagnosis: Normal spleen or accessory spleen" (fig. 1).

COMMENT

The increase in size of the scrotal mass following mumps is of interest and not readily explained. An x-ray of the abdomen after operation showed the spleen to be present in the usual location and of normal size.

SUMMARY AND CONCLUSIONS

A case of spleen in the scrotum, believed to be the fourteenth reported one, is presented. The possibility of splenic tissue being present in the left scrotal compartment must be considered in the differential diagnosis of a mass in that location. Any condition leading to splenomegaly may be reflected in such scrotal enlargement.

The author wishes to thank Doctors W. Rose of Buells' Corners, N. Y. and K. Mitton, E. Kellert and G. Parkhurst of Schenectady, N. Y. for making the presentation of this case possible.

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SCROTAL CALCIFICATION DUE TO MECONIUM PERITONITIS

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The purpose of this discussion is to clearly demonstrate that meconium peritonitis may involve the urogenital system. Diseases of meconium, i.e., meconium peritonitis and meconium ileus, are well documented pathological entities. We do not intend, in this communication, to completely review all of the work concerning these subjects since two outstanding papers are readily available, one by Boikan,[1] and the other by Bruwer and Hodgson.[2] We do intend, however, to recapitulate some of their ideas so that we can formulate the relationship of scrotal calcification due to meconium peritonitis. To this will be correlated certain fetal developmental and physiological premises.

Meconium peritonitis is a sterile, chemical, peritoneal inflammation caused by perforation of the intestine and extrusion of meconium into the peritoneal cavity. It usually occurs during the later half of fetal life. Many factors may be responsible for the intestinal perforation such as atresia of the bowel, volvulus, and peritoneal fibrous bands. These are all anatomical intestinal obstructions. Pancreatic insufficiency, resulting from stenosis of the pancreatic duct, pancreatic fibrosis or cystic disease of the pancreas is of prime importance. Congenital biliary atresia, another related etiological agent, must also be considered. The modus operandi of all of these causative diseases will be considered shortly. It should be pointed out that many times meconium can be present in the peritoneal cavity from intestinal perforation, with subsequent complete healing of the ruptured intestinal wall, leaving no evidence as to why the perforation occurred or to the location of its occurrence.[3, 4]

An associated, and at times, inseparable disease should be briefly mentioned, meconium ileus. Here we have intestinal obstruction in the newborn due to the inability to pass meconium. Since the same etiological factors may be present in both meconium ileus and meconium peritonitis, the two diseases may be quite similar. Since ileus and peritonitis can occur simultaneously, both names may be applicable. When meconium is present within the peritoneal cavity, as manifest on roentgen examination or pathological study, and there is or was no definite evidence of intestinal obstruction, the name of meconium peritonitis would be more applicable. Conversely, if intestinal obstruction is the main

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The statements and conclusions of this manuscript are those of the authors and not necessarily those of the Medical Department of the United States Navy.

Read at annual meeting, Mid Atlantic Section of American Urological Association, Washington, D. C. April 21, 1954.

[1] Boikan, W. S.: Meconium peritonitis from spontaneous perforation of ileum in utero. Arch. Path., 9: 1164–1183, 1930.

[2] Bruwer, A. and Hodgson, J. R.: Intestinal obstruction in fibro cystic disease of pancreas. Am. J. Roentgenol., 69: 14–21, 1953.

[3] Low, J. R., Cooper, G., Jr. and Cosby, L., Jr.: Meconium peritonitis. Surgery, 26: 223–228, 1949.

[4] Packard, G. B. and Reynolds, L. E.: Meconium peritonitis. Ann. Surg., 133: 548–554, 1951.

clinical finding in a newborn, and meconium as a result is deposited on the peritoneal surfaces, then it would appear that meconium ileus would be a better term. In any event, these terms are not clearly defined in the literature.

PHYSIOLOGICAL CONSIDERATIONS RELATED TO MECONIUM

The fetus in early uterine life can swallow. Most of the swallowed material is amnionic fluid which contains lanugo, sebaceous material and desquamated squamous epithelial cells from the skin. Lining cells cast off from the gastrointestinal tract, pancreas and liver, along with bile and pancreatic secretions, are also present.[5] Chemically, the meconium is composed of protein, fats, cholesterol, mucin, stearic acid, and salts.[1] The water from this amnionic fluid is absorbed in the small intestine; the resulting substrate is a black viscid substance. Peristalsis is an important factor in the propulsion of meconium along the intestinal lumen. Peristalsis begins in about the third fetal month. The meconium reaches the ileocecal region about the fourth month and the rectum about the fifth month. During fetal life under normal conditions, the meconium remains within the intestinal lumen. Normally meconium has a fairly soft consistency. If the fluidity changes, meconium becomes putty-like, sticky, and tenacious. The pancreas appears to be the most important organ governing its consistency. In the absence of pancreatic enzymes, as found in pancreatic fibrosis, the meconium becomes so firm that peristalsis cannot propel it through the intestines. Farber[6] has taken meconium, recovered at operations and at autopsy, from patients with meconium ileus and found that mixing it with concentrations of pancreation of 1 per cent to 10 per cent at 37.5°C resulted in a semifluid state. This simple but important observation leaves little doubt that pancreatic secretions are of prime importance in governing the physiological viscosity of meconium. The other generally accepted method that causes inspissated meconium is abnormal water absorption from the intestinal tract. If a congenital obstruction, for example, existed in the lower ileum, the meconium could not pass; and as it accumulated proximal to the obstruction, the water that was absorbed could leave the meconium more solid than fluid. It has also been suggested that the fetus may not normally ingest an adequate amount of amnionic fluid, thereby resulting in formation of meconium of an abnormally firm consistency.

FACTORS CONCERNED WITH THE ETIOLOGY OF MECONIUM PERITONITIS AND MECONIUM ILEUS

It may be again emphasized that no one abnormality is always the cause of meconium peritonitis or meconium ileus. All of the following mechanisms have been observed and recorded in the literature. Each will be discussed separately.

PANCREATIC DISEASE

It appears that trypsin, lipase, amylase, chymotrypsin, renin and maltase are the essential excretory pancreatic enzymes that have their actions on intestinal contents.[7] In the fetus, trypsinogen, which later becomes trypsin, and lipase have been found during the fourth fetal month; and it has been suggested that they may be present earlier. These digestive enzymes are believed to be responsible for keeping the meconium at a normal consistency. Any pathological process that would diminish the amount or prevent the pancreatic secretion from gaining entrance into the duodenum could be the direct cause of inspissated meconium. In general, there are two mechanisms by which we can explain a lack of pancreatic juice in the small intestine; and both of these methods are proven entities.

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[5] Potter, E. L.: Pathology of the Fetus and the Newborn. Chicago: Year Book Publishers, Inc., 1953, pp. 297-307.

[6] Farber, S.: Relation of pancreatic achylia to meconium ileus. J. Pediat., **24**: 387-392, 1944.

Stenosis of the main pancreatic duct. Kornblith and Otoni[8] have described, in complete detail, a 5-day-old infant with meconium ileus associated with congenital stenosis of the main pancreatic duct. The duct proximal to the stenosis was dilated and the pancreas microscopically presented dilation of the terminal ducts with flattening of the acinar cells and marked fibrosis. They reasoned that the meconium was thickened from lack of pancreatic secretion. Its propulsion along the gastrointestinal tract was stopped at the ileocecal region and hepatic flexure, which are considered to be points of physiological narrowing. Perforations occurred due to increased intraluminal pressure from intestinal obstruction. The intestinal contents including meconium escaped into the peritoneal cavity, resulting in peritonitis. Hurwitt and Arnheim[9] reported a similar case in which the main pancreatic duct was stenotic. They further demonstrated that the stenosis is due to a "focal defect" during the development of the duct rather than early epithelial proliferation with failure of canalization as occurs in the other portions of the gastrointestinal tract.

Cystic fibrosis of the pancreas. With this disease, we again have one denominator, a diminished to absent pancreatic secretion. The lack of pancreatic juice is due to an intrinsic obstruction of the smaller pancreatic ducts with inspissation of the secretion in the acini resulting in pancreatic fibrosis.[10] Others[9] believe that parenchymal fibrosis which causes the narrowing of the smaller ducts can result in obstruction and therefore a lack of pancreatic juice. Sako[10] reported 6 cases that are in this category. Farber[11] maintains that cystic fibrosis which can result in pancreatic achylia can cause meconium ileus if the pancreatic insufficiency is present before birth. If the achylia develops in the neonatal period, these patients will develop celiac syndrome. Cystic fibrosis of the pancreas is believed to be a systemic disease.[12] The pulmonary system and portions of the gastrointestinal tract, other than the pancreas, may be involved. The secretory epithelial glands of these organ systems are apparently deficient.

[7] Best, C. H. and Taylor, N. B.: Physiological Basis of Medical Practice. Baltimore: Williams and Wilkins, 1950, 5th ed, pp. 529–530.

[8] Kornblith, B. A. and Otani, S.: Meconium ileus with congenital stenosis of main pancreatic duct. Am. J. Path., 6: 249–262, 1929.

[9] Hurwitt, E. S. and Arnheim, E. E.: Meconium ileus associated with stenosis of pancreatic ducts; clinical, pathological and embryologic study. Am. J. Dis. Child., 64: 443–454, 1942.

[10] Sako, W.: Meconium ileus. New Orleans Med. & Surg. J., 102: 75–77, 1949.

[11] Farber, S.: Pancreatic function and disease of early life. Arch. Path., 37: 238–250, 1944.

[12] Zuelzer, W. W. and Newton, W. A., Jr.: Pathogenesis of fibrocystic disease of pancreas. Pediatrics, 4: 53–69, 1949.

Therefore, the combined lack of pancreatic and intestinal secretion may be factors which augment the formation of thick, putty-like meconium.

BILIARY ACHYLIA

Unanimous agreement is not found again when we consider the biliary achylia as the etiology. Dodd,[13] Landsteiner,[14] and Potter,[5] believe a diminished amount of bile and pancreatic secretion together are probably necessary to produce a lack of fluidity to meconium. Fanconi[15] presented a case of meconium ileus in which the pancreas was normal, but the liver showed evidence of aplasia of the larger ducts. Without bile mixing with the intestinal contents, a "fatty" meconium was produced. Farber[6] has stated that meconium ileus was not found in 34 infants with proven congenital atresia of the bile ducts. He believes where the pancreas was reported as normal, in cases of true meconium ileus, that unrecognized acinar lesions may exist. This is further explained by stating that in cases where there is obstruction of the small pancreatic ducts, the larger pancreatic ducts are normal and no pancreatic fibrosis is found. In any event, biliary achylia has been shown to be a cause of inspissated meconium resulting in an ileus. Admittedly, this etiology is not common.

MECHANICAL INTESTINAL OBSTRUCTION

Neuhauser[16] has reported 3 cases of intestinal obstruction from atresia of the small intestine. The specific areas of involvement were in the duodenum, jejunum, and terminal ileum; and these were all proven at operation. Areas of scattered calcification in the abdomen were observed on the roentgenograms. Pathologically, these calcific deposits were due to meconium that has been extruded through the intestinal wall and had subsequently undergone calcification. The calcification is believed to be due to the precipitation of calcium by the broken down fatty constituents of meconium.[1] Since it was not possible at time of operation to determine the sight of perforation, it was concluded that the perforation occurred during intrauterine life, probably after the fifth fetal month and underwent complete healing. Areas of the pathological specimens show the calcified plaques to be composed of cornified epithelial cells. The calcium may be within the bowel wall and lumen of the intestine. Many of the calcium deposits were imbedded in adhesions between the intestine and parietal peritoneum. Roentgenograms of a newborn with the following findings are characteristic of meconium peritonitis: 1) dilated loops of bowel with air and fluid levels in the erect position, and 2) one or more calcific plaques within the abdomen which may be within the bowel, the intestinal wall, or on the peritoneal surface. It has been generally assumed that intestinal atresia occurred because the intestinal epitheloid proliferation later failed to recanalize.

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[13] Dodd, K.: Intestinal obstruction due to meconium ileus in newborn infant. J. Pediat., 9: 486–491, 1936.

[14] Landsteiner: (Cited by Dodd.[13])

[15] Fanconi: (Cited by Brewer and Hodgson.[2])

[16] Neuhauser, E. B. D.: Roentgen diagnosis of fetal meconium peritonitis. Am. J. Roentgenol., 51: 421–425, 1944.

A somewhat similar situation to the above may exist with an entirely different logical explanation. Zuelzer and Newton[12] have clearly demonstrated that intestinal atresia may be a result of impaction of meconium, making the atresia a secondary effect of inspissated meconium. Their microscopic studies reveal that the atresia resulted from impacted meconium with necrosis of the mucosa followed by organization and obliteration of the lumen. The gross findings at operation and autopsy would help confirm these observations. Time and time again, observers have noted meconium to be sticky and tenacious. It has been found to be inseparable from the intestinal wall, and attempts at separation have caused the involved bowel wall to break.[16] Microscopic observations offer further correlation. The diffuse inflammatory reaction throughout the peritoneal cavity and intestinal walls can be followed by organization resulting in massive areas of fibrous tissue and calcium plaques.[3] Thus the segment of the intestinal tract which was blocked by inspissated meconium becomes a fertile field for marked fibrosis, which, in turn, could be extensive enough to cause obliteration of its lumen. This type of atresia is referred to as an organic atresia in differentiation from a developmental atresia.

Other factors responsible for intestinal obstruction are clearly tabulated by Levy.[17] All of these cases were proven to be fibrocystic disease of pancreas and many of them had associated abnormalities such as fibrous bands, atresia of the small intestine, and volvulus. He believes that the meconium ileus had its origin from pancreatic insufficiency and the associated abnormalities may be coincidental. In any event, there does exist the possibility that these abnormalities may be considered as contributory factors in the production of intestinal obstruction. Packard and Reynolds[4] recently have reported that volvulus, secondary to malrotation of the small intestine, can produce mechanical intestinal obstruction resulting in meconium peritonitis. In their case, there was no evidence of pancreatic insufficiency at autopsy. Intestinal obstruction followed by intestinal perforation was the only discernible causative factor of meconium peritonitis.

CASE REPORT

R. A. C., a 3½ month-old white, male infant was admitted to the hospital on November 9, 1953 for study and treatment of multiple small intrascrotal masses. The newborn record revealed that some enlargement of the scrotum was noted at birth, but no definite pathological change was recorded. A normal meconium stool was passed on the first neonatal day. The parents had noted the scrotal masses on the fifth neonatal day and stated that there had been no change in their size or character. The child had developed normally since birth. The family history was not relevant. The Rh factor in both father and mother was positive. Physical examination was normal except for the scrotum which was slightly enlarged and contained numerous irregular sized, firm nodules, some freely movable and some which were fixed in the scrotal tissue. A complete blood count, bleeding and coagulation time, Kahn test, and an urinalysis were all normal or negative. Examination of the stool for tryptic activity was posi-

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[17] Levy, E.: Case of fibrocystic disease of pancreas with intestinal obstruction. Arch. Dis. Child., 26: 335–339, 1951.

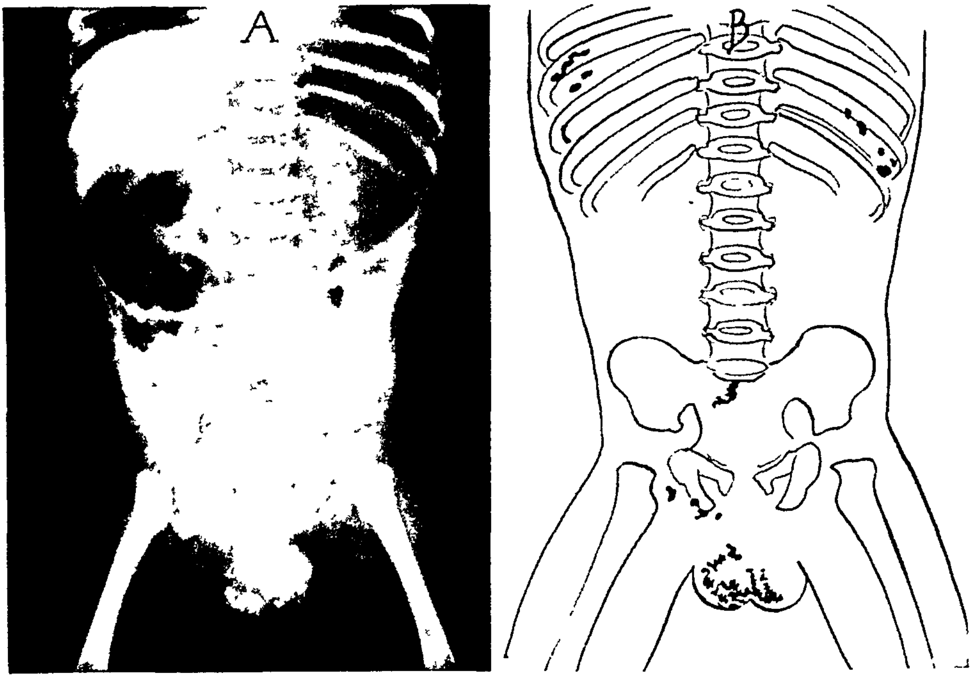

Fig. 1. Roentgenogram of abdomen shows normal upper urinary tract. Flake-like calcific deposits are observed over superior and lateral margins of liver and capsule of spleen. Calcification is present overlying sacrum, along right inguinal canal and in scrotum. Large, distended stomach was induced by oral feeding to more clearly visualize upper urinary tract. *B*, schematic drawing *A* shows areas of calcification in black.

tive;* an upper gastrointestinal tract series and small bowel study were normal. A plain x-ray revealed multiple small areas of calcification over the dome of the liver and spleen, over the sacral region, along the right inguinal canal, and in the scrotum. An excretory urogram revealed a normal upper urinary tract (fig. 1).

On November 12, 1953, the right lower inguinal canal and the right scrotum were explored. This revealed several small, yellowish, calcified appearing nodules studded along the spermatic cord. These were easily resected. Lying free within the tunica vaginalis were five cystic bodies varying in diameter from 0.5 cm. to 1.5 cm. These cysts were filled with many small, yellowish appearing bodies (fig. 2). The tunica vaginalis itself was studded with many of these small calcified bodies and there was considerable tissue reaction in the involved areas. There was a collar of involved tissue surrounding the upper pole of the testis. After the involved areas were resected, the tunica vaginalis of the left scrotum could be visualized and through it, one could see several of the previously described calcific bodies. No attempt was made to resect these. The testis was replaced in the right scrotum and the wound closed.

Sections of the calcific bodies revealed a fibrous capsule containing many vessels. The central portion of the bodies was composed of a loose type of tissue containing strands of fibrous tissue. Scattered throughout were areas of calcification. An occasional squamous cell was noted as well as macrophages containing a brown pigment.

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* Anderson-Early gelatin test for tryptic activity[18].

[18] Anderson, D. H. and Early, M. V.: Method of assaying trypsin suitable for routine use in diagnosis of congenital pancreatic deficiency. Am. J. Dis. Child., **63**: 891–893, 1942.

Chemical analysis of one of the calcific bodies for bile was positive.

The pathological impression was: calcified bodies, scrotum, compatible with meconium peritonitis.

The postoperative course was uneventful.

DISCUSSION

Our purpose is to correlate the embryological descent of the testes to the disease of meconium peritonitis. Arey[19] most clearly explains scrotal and testicular development. About the sixth fetal month, two peritoneal sac-like pockets have formed on the ventral abdominal wall. These pouches are called processus vaginalis and they are at the site of the internal abdominal rings (fig. 4, *A*). Each processus vaginalis pushes obliquely through the anterior abdominal wall (inguinal canal) and then inferiorly to invade the scrotum about the seventh fetal month (fig. 4, *B*), concomitantly, the testes are descending posterior to the peritoneum along the posterior abdominal wall. Attached to the most inferior portion of each testis is the gubernaculum which *extends through the inguinal canal* into the scrotum. During the seventh fetal month, the gubernaculum shortens; and some time between the seventh and ninth fetal months, the testes enter the scrotum (fig. 4, *C*). It is important to remember that the testes are covered with peritoneum before and during descent. The stalk of the original peritoneal sac, the processus vaginalis, starts to obliterate about the ninth fetal month; and the remaining portion around the testes, the tunica vaginalis, remains (fig. 4, *C*).

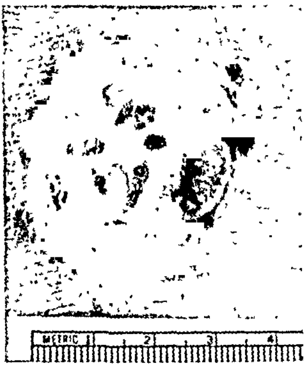

FIG. 2. Gross specimen reveals excised sac studded with numerous small, firm, grayish-yellow nodules. Lying free within sac are oval shaped, cystic lesions filled with yellowish colored firm granules.

Since we have established that meconium is present in the gastrointestinal tract during latter half of fetal life; and that meconium peritonitis may occur

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[19] Arey, L. B.: Developmental Anatomy. Philadelphia: W B. Saunders Co., 1947, 5th ed, pp. 300–301.

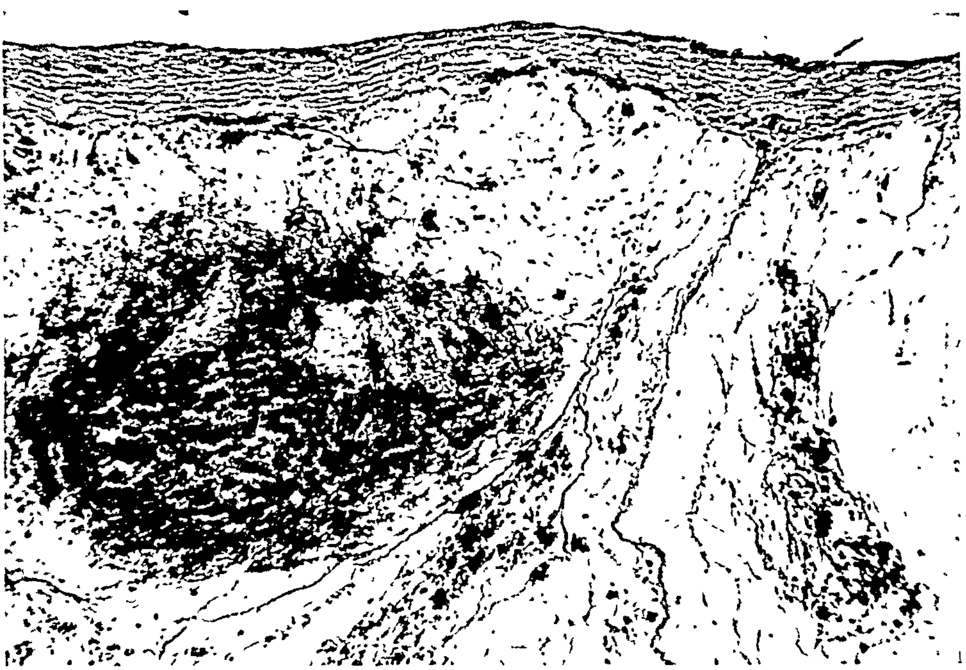

FIG. 3. Microscopic section of calcific body reveals fibrous capsule inclosing strands of loose fibrous tissue, areas of calcification, and occasional macrophages filled with brown granules.

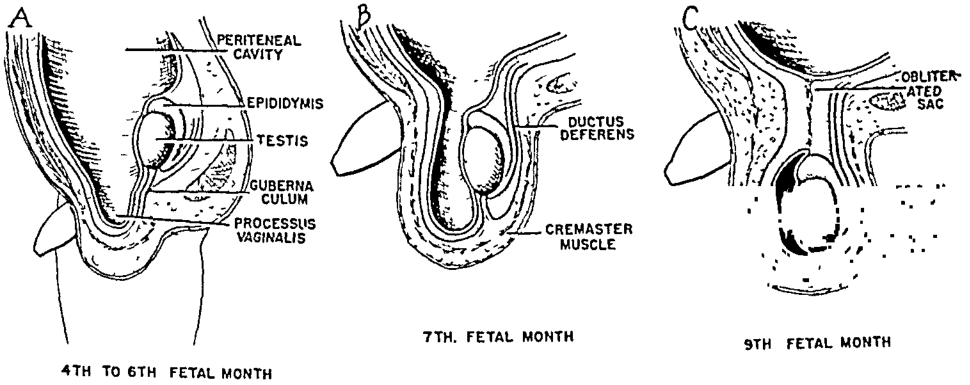

FIG. 4. *A*, schematic drawing showing relationship of testis to posterior abdominal wall. Processus vaginalis is forming. (Copied from Arey's *Developmental Anatomy.*) *B*, schematic drawing showing processus vaginalis invading scrotum. Note: Peritoneum of abdomen is continuous with peritoneum overlying testis and peritoneal extension into scrotum. (Copied from Arey's *Developmental Anatomy.*) *C*, schematic drawing showing remaining peritoneal extension, tunica vaginalis. Obliterated sac was previously stalk of process vaginalis. (Copied from Arey's *Developmental Anatomy.*)

during this same time, we therefore have a corresponding time relationship between the known occurrence of meconium peritonitis and testicular descent into the scrotum. The other important factor is that peritoneal evagination into the inguinal canal and scrotum is in close anatomical approximation to the peritoneal surfaces of the intestine. It would, therefore, be logical to assume that the calcific masses seen along the inguinal canal and in the scrotum on the roentgenograms, which were subsequently found to be meconium by microscopic section, represent a manifestation of the diffuse generalized peritonitis. We have further proof that the calcified material originated in the gastrointestinal tract, because bile was found in this material by chemical analysis Some of the calcified meconium was in the wall of the interscrotal septum, and from this, it may be assumed that during the healing process of the peritonitis, the fibrosis that resulted obliterated portions of the definable limits of the tunica vaginalis Thus, the calcium products could be incorporated into the adjacent fibrous wall As the most proximal portion of the processus vaginalis obliterated, the calcified meconium and peritoneal inflammation in this immediate area was trapped The irritative reaction of the meconium peritonitis was probably slow in subsiding since many of the areas in the scrotum became walled off and cystic masses were thereby formed (fig 3)

We have evidence to believe this case presented extensive abdominal involvement in view of the fact that calcification was observed in the upper abdomen over the capsule of the liver and spleen and in the region of the terminal ileum (fig 1) The etiology of the perforated intestine is not apparent, but the specific area of ruptured intestine healed without sequela, since no evidence of any gastrointestinal disturbance can be obtained in the patient's history Barium studies of the gastrointestinal tract also failed to reveal any suggestive intestinal abnormality

This case is not only unique because of the involvement of the scrotum, but also because it demonstrates that meconium peritonitis may represent a self limited, benign type of disease If the scrotum had not been involved, there would have been no clinical findings to suggest the presence of meconium peritonitis Of the 11 reported cases of meconium peritonitis[2, 3, 16, 20, 21, 22] where calcification was seen on roentgenograms, all of the cases, with one exception, were operated on because of intestinal obstruction This case was reported by Olnick and Hatcher[21] and is very similar to the case we are reporting We therefore believe these 2 cases bridge a gap showing that meconium peritonitis can exist without abdominal symptoms or intestinal obstruction because the intestinal perforation and subsequent healing occurred before birth and no complication or sequela followed

To Neuhauser's roentgenographic findings, we may add 1) calcific deposits observed over the margins of the liver and spleen and in the abdomen in an asymptomatic infant can be due to meconium peritonitis, and 2) calcification within the scrotum associated with multiple areas of abdominal calcification must be considered as resulting from meconium peritonitis

SUMMARY

Meconium peritonitis has been demonstrated to involve the scrotum It is believed that meconium escaped into the abdominal cavity sometime after the fourth fetal month, followed by healing of the perforated intestine The

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[20] Brunkow, C W Nelson G Goodnight, S , Hunter, A and Brunkow, M Fetal meconium peritonitis abscess intestinal obstruction, disappearance of radiopaque meconium bodies West J Surg **57** 424–429, 1949

[21] Olnick H M and Hatcher, M B Meconium peritonitis J A M A , **152** 582–584, 1953

[22] Conrad H A and Robbins, F R Congenital atresia of jejunum with meconium peritonitis J Internat Coll Surg **15** 320 327, 1951

sterile peritoneal reaction that followed (meconium peritonitis) resulted in the deposition of calcium within the meconium. The peritoneal surfaces, surrounding the testes, which at this period of development are retroperitoneal, become involved in the generalized peritonitis. As the testis descended to the scrotum, the adjacent peritoneum containing calcific plaques followed. The calcified meconium was then distributed along the inguinal canal and the tunica vaginalis. Other areas of calcification were noted throughout the abdomen, especially on the surfaces of the liver and spleen. This patient demonstrates that meconium peritonitis can be a benign, asymptomatic disease without intestinal symptoms.

The common etiologies are discussed along with the physiological properties of meconium.

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PRIMARY FIBROSARCOMA OF THE TUNICA VAGINALIS

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Although there is no complete agreement concerning the frequency of sarcoma of the tunica vaginalis, a review of the literature indicates that the lesion is rare. Because of this fact, the following case presentation is of interest.

N. M., a white boy 16 years of age, was admitted to the Presbyterian Hospital on May 10, 1953 because of a painless left scrotal mass, progressively enlarging over the previous 2 months. There was an absence of urinary tract complaints and no systemic reaction. There was a history of scrotal trauma while the patient was at play one month prior to onset of the scrotal swelling.

Physical examination revealed a hard tumor mass 3 cm. in diameter medial and superior to the left testicle. The left testicle was apparently normal. The remainder of the examination was entirely negative. The blood pressure was 115/60, and the temperature 98.8 degrees.

Examination of the urine was entirely negative. The erythrocytes were 4.18 million, hemoglobin, 13.5 gm. and leukocytes, 7,100. Roentgen examination of the chest was normal (fig. 1, A).

Operation was performed on May 11, 1953. A high resection of the spermatic cord at the internal inguinal ring was performed with retrograde dissection of the cord and the tunica vaginalis and its contents.

The surgical specimen consisted of a normal testis accompanied by normal epididymis with a tumor mass 1 by 3 by 3.5 cm. in size, hard, irregular, and glistening yellow-white in appearance arising from the tunica vaginalis. The tumor mass was everywhere separate from the spermatic cord, epididymis, and testis (fig. 2). Cut section of the tumor showed a whorled appearance with almost cartilagenous areas without evidence of extension into adventitial tissues of the tunica vaginalis.

Microscopic examination revealed the tumor to be composed of spindle-formed cells interspaced by variable dense and loose stromal elements containing a moderate number of blood vessels. There were areas of considerable variation in size and shape of the tumor cells with numerous atypical nuclear patterns and frequent mitotic figures. The tumor was seen to be growing along the surface of the tunica vaginalis but was sharply demarcated from the adventitial structures (figs. 3 and 4). Microscopic study of the testis, epididymis, and the spermatic cord revealed no involvement in these structures by the tumor. Diagnosis: Fibrosarcoma of the tunica vaginalis.

The postoperative course was uneventful, and the patient was discharged on the fifth postoperative day. Follow-up examinations were without findings until September 25, 1953. At this time, the patient complained of shoulder pain, and roentgen examination of the chest revealed metastastic lesions in the right upper

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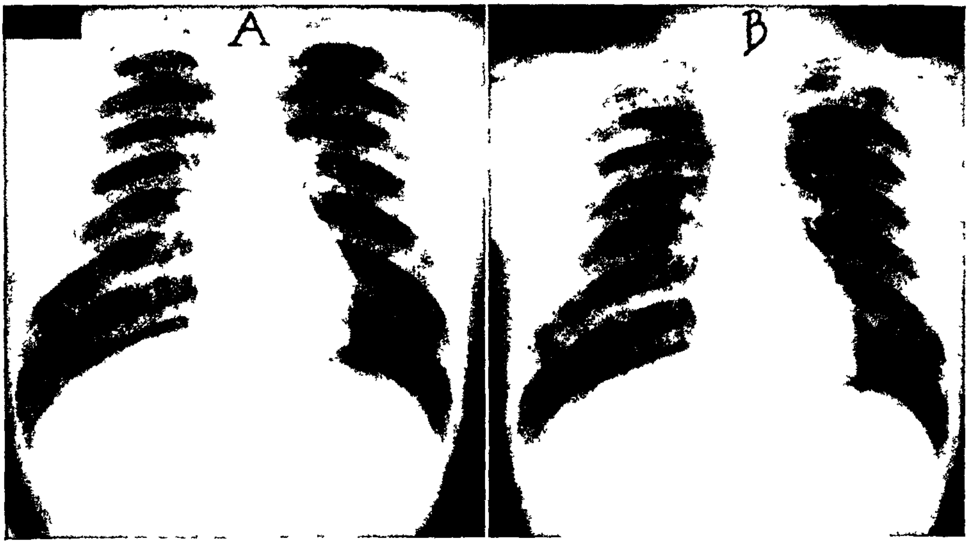

FIG. 1. *A*, normal chest x-ray, May 16, 1953. *B*, metastases in right upper lung and left eighth rib noted September 25, 1953.

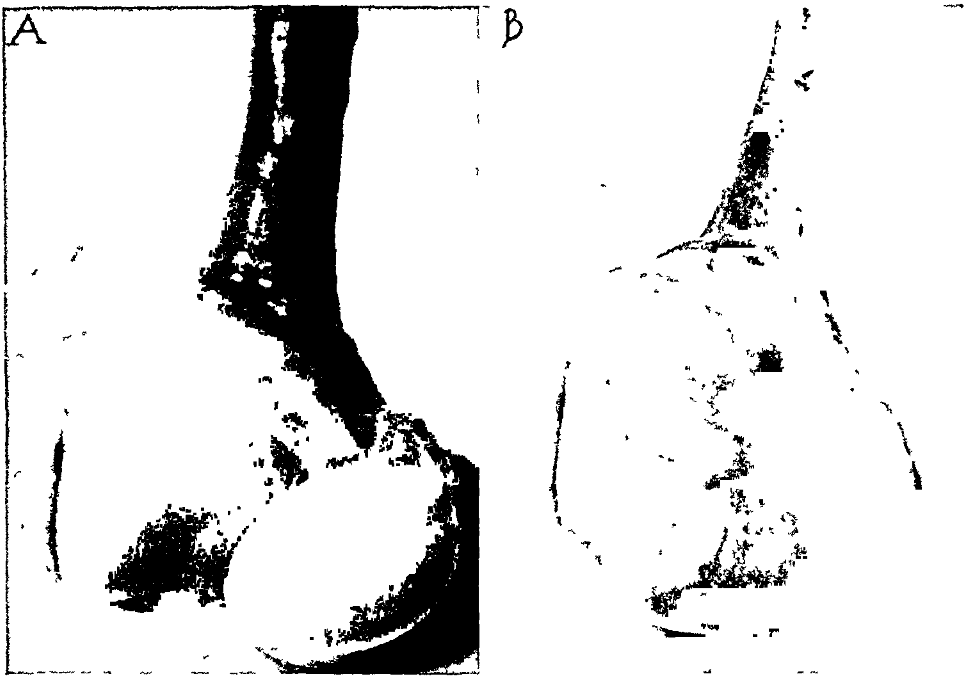

FIG. 2. *A*, gross specimen showing origin of tumor in tunica vaginalis. Testis is grossly separate from tumor. *B*, gross surgical specimen showing epididymis separate from tumor.

lung and the left eighth rib (fig. 1, *B*). The course was rapidly downhill with death occurring on December 29, 1953. There was no evidence of local recurrence. No autopsy was obtained.

There is a marked disparity in reports of various reviews on the frequency of this lesion perhaps because of the extreme difficulty in many instances in distinguishing the true origin of the sarcoma. Numerous authors mention this, and

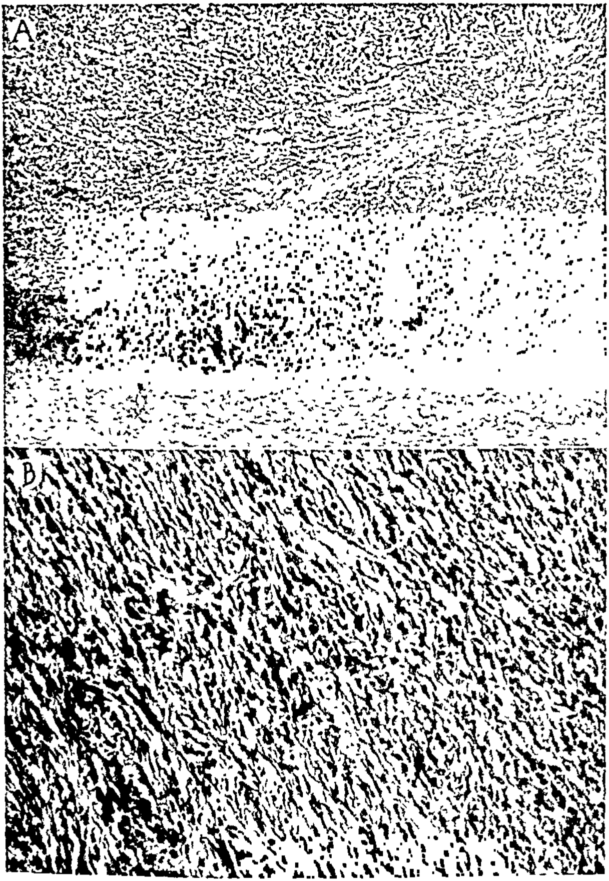

Fig. 3. *A*, typical pattern of fibrosarcoma and sharp demarcation from adventitial tissues. *B*, spindle-form cells with variable dense and loose stromal elements.

Oberndorfer cites several cases in which gross and microscopic examination of the scrotal contents was insufficient to determine the origin of the sarcoma.

Oberndorfer further states that it is only in those tumors occupying the parietal leaf of the tunica vaginalis, well separated from other structures, that may be called true sarcoma of the tunica vaginalis. In addition, the greater or lesser critical appraisal of previously reported cases leads to additions and deletions in the reviews which cause general confusion and finally allow only an approximate estimate of the frequency of the lesion.

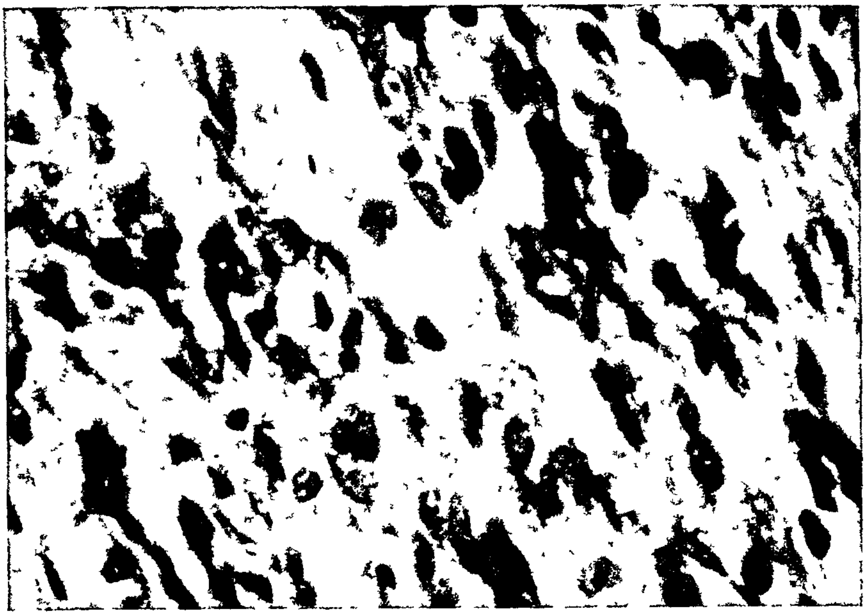

FIG. 4. Note variation in size and shape of tumor cells with numerous atypical nuclear patterns.

Hinman and Gibson in 1924 collected 12 cases of sarcoma of the tunica vaginalis from the literature. One of these was a questionable case of Karewski's, and three cases were reported by Miyata. Rubaschow in 1926 collected 15 cases with only two of the cases credited to Miyata. Thompson (1936) added the reports of Valdoni (1927) and Donati (1934) in a review of tumors of the extra-testicular scrotal contents. Waller cites Trabucco's case (1940) in a 5-year-old boy and in addition cites Graflin's claim of 48 primary sarcomas of the tunica vaginalis collected from the literature.

Quinby (1937) reported a fibrosarcoma originating in the tissues of the scrotum but without a definitive primary site. O'Brien (1942) reported a case of fibrosarcoma of the epididymis, but in the discussion Gilbert suggested that the extreme degree of malignancy was more in keeping with a primary tumor of the "tunics proper or in the tunics of the cord."

In this study it was found that Miyata's 3 cases consisted of sarcoma of the sheath of the spermatic cord, tunic of the epididymis, and tunic of the testes. In all probability, the case of sarcoma of the tunic of the testes is primary in the tunica vaginalis. It is difficult to locate the primary origin of the tumor reported by Karewski (1894) involving the testes, epididymis, and spermatic cord. Graflin's collection of 48 cases (1941), as cited by Waller, include other intrascrotal origins in addition to the tunica vaginalis.

In all, a total of 25 cases of primary fibrosarcoma of the tunica vaginalis, including this report, have been recorded.

Carcinoma of the tunica vaginalis is extremely rare. Waller reviewed the literature and reported a case of dysontogenetic tumor of the tunica vaginalis with malignant epithelial elements predominant. Darget and Penaud reported a case of multiple papillary epithelioma of the tunica vaginalis, and Chauvenet and Bonnard in the same year (1937) reported a similar type tumor

Benign lesions of the tunica vaginalis are by far predominant over malignant growths These include fibromas (56 cases), adenomas (13 cases), lipomas (3 cases), and vascular tumors (4 cases)

Primary sarcoma of the tunica vaginalis is predominantly found in the younger age groups in contradistinction to sarcoma of the spermatic cord which occurs rarely in young individuals However, these tumors have been found in individuals from 2½ to 76 years of age

There is little to add in the technique of differential diagnosis except to reiterate the technique of Valdoni of injecting air within the tunica vaginalis and performing pneumo roentgenograms He feels that this technique makes differentiation of intrascrotal tumor masses relatively simple Careful examination preoperatively to distinguish the organ of origin and to evaluate the duration and rate of growth are of value in determination of the operative procedure of choice A rapidly growing mass, whether a new growth or a spurt in growth of an old mass, should certainly be considered as a possible malignant lesion

The choice of treatment appears to be complete *en masse* excision with re section of the vascular supply as far as possible from the tumor Taylor and Nathanson in a review of 246 patients with encapsulated fibrosarcoma of soft tissues found 62 per cent had been treated because of local recurrence In the primary initial lesions of their series, local control of the disease was effective in only 50 per cent of those treated Lymphatic metastases have been noted in only 8 per cent of the patients in a series of 256 cases of primary fibrosarcoma of soft tissues This would not seem to warrant routine retroperitoneal lymph node dissection in primary fibrosarcoma of tunica vaginalis The primary mode of metastases is vascular and seemingly is related more to local recurrence than to the primary incidence of the disease Radiation therapy is generally conceded to be of little value in the treatment of fibrosarcoma of soft tissues

CONCLUSIONS

A case report of primary fibrosarcoma of the tunica vaginalis with a review of the literature is presented

Preoperative and pathological differentiation of the origin of intrascrotal extratesticular malignant lesions is difficult and in many instances impossible

Operative procedure of choice is *en masse* local excision, including adventitial tissue with high severance of the spermatic cord Radiation is of little value, and in view of the infrequent occurrence of lymphatic metastatic spread retro peritoneal lymph node dissection is not warranted

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PROSTATECTOMY ON PATIENTS WITH HEART DISEASE

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In consequence of the development within the techniques of operation and anesthesia, shock treatment, fluid and electrolyte treatment, checking of infectious diseases, and the understanding of the thrombotic lesions, a steadily increasing number of patients are now being submitted to prostatectomy, who previously were thought unfit for the operation The object of the present investigation has been to throw a light on the risk involved by prostatectomizing patients with heart disease and, if possible, to draw conclusions from this

The material comprises all the patients submitted to prostatectomy for benign prostatic hypertrophy in the urological department D, Bispebjerg Hospital, between January 1, 1947 and March 31, 1952 The majority of the patients admitted to this department belong to the socially and economically badly situated population of the capital

A fairly large proportion of these patients suffered from heart disease In a number of cases the preoperative state was assessed and the treatment, as well as the treatment of possibly occurring postoperative complications were decided on through collaboration of urologist, anesthetist, and internist

The criteria of heart disease appear in table 1

A history of or the presence of one or more of the indicated cardiac symptoms placed the patient concerned in the cardiac group The heart diseases were in practically all cases of an arteriosclerotic and/or hypertensive nature The group is very inhomogeneous with regard to the severity of the heart disease, ranging from patients with very mild or no subjective cardiac symptoms to patients with severe cardiac insufficiency

Figure 1 illustrates, for the two groups with and without heart disease respectively, the distribution in age classes, incidence of overweight, hypertension (systolic pressure over 160 mm Hg and/or diastolic over 100 mm Hg), and other diseases (diabetes mellitus, pulmonary diseases, hemiparesis, peptic ulcer, joint lesions, and others) The patients of the cardiac group were in the main somewhat older than those of the normal group, and hypertension was considerably more frequent in the former, whereas overweight and other diseases were only slightly more frequent in the former than in the latter

In figure 2 the groups are compared with regard to methods of operation and anesthesia It is seen that the groups do not differ essentially The heart disease has, in other words, not given occasion to special methods of operation or anesthesia Figure 2 shows further that three methods of operation were employed, viz , one stage transvesical prostatectomy, Millin's operation, and two stage transvesical prostatectomy Spinal analgesia was performed with cincain-glucose (heavy solution), balanced anesthesia with a combination of pentothal, pethidine, nitrous oxide, and relaxant, and inhalation anesthesia with N_2O ether or O_2-cyclopropane, with or without relaxant

TABLE 1. *Cardiac symptoms in group of 178 patients with heart disease*

Total		*440*
No heart disease	Group A	262
Heart disease	Group B	178

Symptoms of heart disease in group B

Case History:	Cardiac insufficiency		35
	Angina pectoris		29
	Previous coronary thrombosis		3
Present Status:	Cardiac insufficiency		20
	Cardiac enlargement		44
	Dilatation of the aorta Calcification of the aorta		45
	Pathological ECG		123
	Auricular fibrillation	9	
	Other arrhythmias	19	
	PQ > .20 sec.	8	
	Bundle branch block	8	
	Anormal T-waves	80	
	Other variations from normal	33	
	(Deviation of ST)		
	(Low voltage)		
	(Prominent Q-waves)		
	(Variations in QRS)		

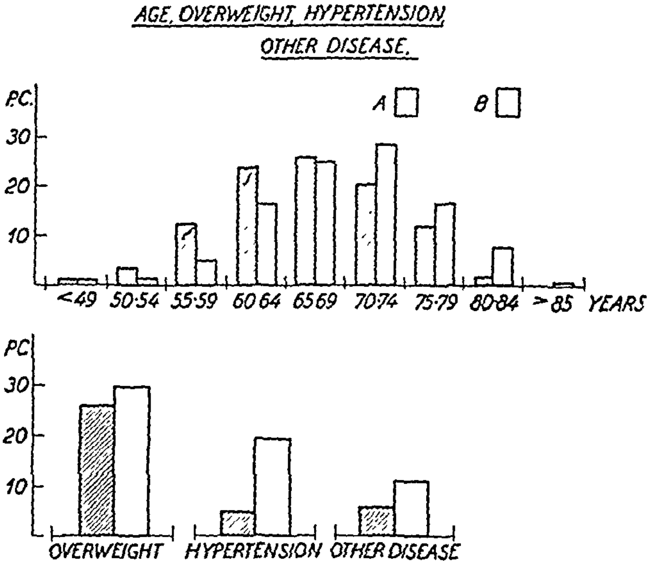

FIG. 1. Distribution in age-classes, and frequencies of overweight, hypertension, and other complicating diseases in two groups. *A* (solid column), without heart disease. *B* (open column), with heart disease.

Table 2 illustrates the mortality rates and the direct causes of death in the two groups. Total mortality 3.9 per cent, in the normal group 1.9 per cent, and in the cardiac group 6.7 per cent. Half of the deaths (6 out of 12) in the cardiac group were due directly to the heart disease, while none of the deaths in the normal group were attributable to cardiac disorder.

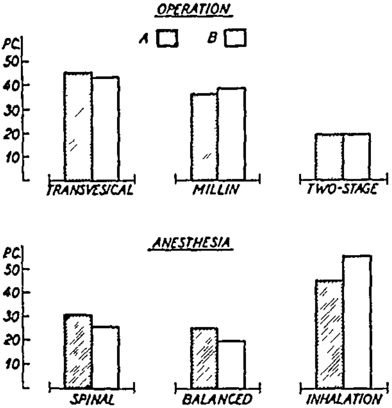

FIG. 2. Methods of operation and of anesthesia in two groups. *A* (solid column), without heart disease. *B* (open column), with heart disease.

TABLE 2 *Mortality rates and direct cause of death in two groups*

Mortality Rate

Total: 440 cases with 17 deaths, 3.9%
Patients without heart disease: 262 cases with 5 deaths, 1.9%
Patients with heart disease: 178 cases with 12 deaths, 6.7%

Causes of Death

	Congestive Heart Failure	Coronary Thrombosis	Pulmonary Embolus	Shock	Cerebral Hemorrhage	Uremia	Hematemesis
Without heart disease			3	1		1	
With heart disease	5	1	3	1	1		1

TABLE 4

	Total	Complication in	of whom died
Without heart disease	262 pts	50 (19%)	4 (8%)
With heart disease	178 pts.	46 (26%)	10 (22%)

To these may be added one death in the normal group and two in the cardiac group of patients who presented none of the stated postoperative complications.

The 12 deaths in the cardiac group have been set out in table 3 for further illustration of the indirect causes of death.

The preoperative cardiac state did not suggest a particularly high risk for these 12 patients. The severity and combinations of the cardiac symptoms did not differ essentially from those of the remaining patients in the cardiac group. On the other hand, we found a remarkable accumulation of postoperative complications, surgical as well as phlebothrombosis and pulmonary complications.

TABLE 3. *Twelve deaths in cardiac group recorded for comparison between preoperative cardiac state and postoperative complications*

Case	Age	Overweight	Hypertension	Other disease	Preoperative Heart Symptoms					Surgical complications	Phlebothrombosis	Pneumonia, atelectasis	Postoperative cardiac failure	Cause of Death
					Cardiac failure in case history	Angina pectoris	Present cardiac failure	Cardiac enlargement	Pathological ECG					
1507/51	64	+							Anormal T-waves	Ileus			+	Cardiac failure
669/49	70	+	+		+					Hemorrhage			+	Cardiac failure Shock
4322/47	58					+				Uroplania	+	+	+	Cardiac failure Uremia
1928/47	66								Wilson block anormal T_2	Gastric dilatation			Auricular fibrillation	Cardiac failure
1561/48	74	+		+					Anormal T-waves				+	Cardiac failure
2510/51	66	+		+				+			+	+	Coronary thrombosis	Cardiac failure
1578/51	66							+			+			Pulmonary embolus
4153/49	75					+					+			Pulmonary embolus
2866/51	75			+			+	+	Auricular fibrillation		+	+		Pulmonary embolus
3018/47	59								Anormal T-waves	Hemorrhage				Hematemesis
2712/47	64				+					Gastric dilatation				Shock Uremia
4172/48	67		+	+	+		+		Anormal T-waves					Cerebral hemorrhage

The significance of the complications for the mortality rates in the two groups appears in table 4, which shows the number of patients in each group (with and without heart disease) who had one or more of the following postoperative complications: hemorrhage (requiring renewed surgical intervention in the form of change of catheter, endoscopic evacuation, cystotomy or cystostomy), paralytic ileus, phlebothrombosis, pulmonary embolism, pneumonia, atelectasis.

It is seen that the frequency of postoperative complications was only slightly higher in the group with heart disease (26 per cent) than in that without (19 per cent). The mortality rate, on the other hand, among the patients with complications was much higher in the group with heart disease (22 per cent) than in the other group (8 per cent).

We must therefore conclude that the risk for the cardiac patients is due mainly to the fact that the postoperative complications, when present, are more fatal for the patients with heart disease than for those without. The chance of developing postoperative complications of the above kinds is only slightly higher among the former than among the latter.

DISCUSSION

Even though the mortality rate in the cardiac group in the present series was just over three times higher (6.7 per cent) than in the normal group (1.9 per cent), the number of patients who died was yet so small that the operation must have been justified in spite of the heart disease, if at all one undertakes to prostatectomize patients with heart disease to relieve their painful and troublesome condition. The fact that the cardiac symptoms often decline following prostatectomy, which removes the urinary troubles and cases of retention, thus allowing sleep to continue without being interrupted by frequent micturition, likewise argues in favor of performing prostatectomy on patients with heart disease. This has also been emphasized by Bacon, Kretschmer, and Woodruff (1931).

Assessment of the risk for cardiac patients is, from a cardiological point of view, based more on a clinical evaluation of the general condition and the degree of insufficiency than on the results of electrocardiography and x-ray examination of the heart. Such examinations generally show nothing about the risk involved by operation on a patient with heart disease, except in the few cases where only electrocardiography can give information on the presence or not of a fresh coronary occlusion. Our series of cardiac patients could not be divided either in different risk groups on the basis of these methods of examination. Finally, we must bear in mind that a normal electrocardiogram and normal x-ray findings do not preclude cardiac disorders. There may previously have been a tendency to overrate the value of these methods of examination in relation to assessment of the risk of operation, in the way that especially changes in the electrocardiogram were judged so severe that the surgeon was unwilling to operate upon the patient.

At present prostatectomy is contraindicated only in cases of severe insufficiency at rest, which does not respond to digitalis and diuretics, as well as of coronary occlusion within the past 2 or 3 months. Overweight and other complicating diseases, especially pulmonary affections, simultaneously with the heart disease seem to add somewhat to the risk.

These views are in keeping with those advanced by Kretschmer and Butler (1948), Galbraith (1948), Gammelgaard (1950), and Ostenfeld (1951).

To obtain a further reduction of the mortality rate it seems essential to prevent postoperative complications, which may prove fatal to patients with heart disease.

SUMMARY

The risk involved by submitting patients with heart disease to prostatectomy is illustrated by comparing a group of 262 patients having no heart disease with a group of 178 patients suffering from arteriosclerotic and/or hypertensive cardiac disorders. The operative mortality rate in the group without heart disease was 1.9 per cent and in that with heart disease 6.7 per cent. The frequency of postoperative complications was only slightly higher in the cardiac group (26 per cent) than in the normal group (19 per cent), whereas the mortality rate among the complication-affected patients was considerable higher in the former group (22 per cent) than in the latter (8 per cent).

At present prostatectomy is contraindicated, on a cardiac basis, only in cases of severe refractory insufficiency at rest and of fresh coronary occlusion (within 2 months).

To obtain a further reduction of the mortality rate among patients with heart disease it is essential to prevent postoperative complications, such as postoperative hemorrhage, phlebothrombosis, pulmonary complications, and paralytic ileus.

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LYMPHOSARCOMA OF THE TESTIS

DEAN C VARNEY

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Although commonly accepted as a metastatic phenomenon, lymphosarcoma of the testis should be considered as a possible clinical entity

Since Malassez's original report in 1877, approximately 30 cases have been reported in the British and American literature While seldom evident as the only clinical manifestation of the disease, it constitutes the most common metastatic tumor of the testis Several observers claim that it may originate primarily in that organ In 1941 Helfert and Pinck were able to collect reports of less than 50 cases of metastatic testicular tumors Willis, in a review of over 500 cases of consecutive cancer necropsies, reported 2 cases, while Watson et al , in a monumental study of 1073 cases of lymphoblastomas, of which 456 were lymphosarcomas, found 75 of the latter invading the genitourinary tract and only 2 involving the testes Dockerty and Priestley noted only 4 instances of lymphosarcoma in a survey of 400 cases of testicular malignancies

It is the purpose of this report to present 5 cases of proven lymphosarcoma of the testis, and to discuss certain diagnostic and therapeutic considerations in the management of the disease

CASE REPORTS

Case 1 G W , a 57-year old white man, entered the hospital April 13, 1950 complaining of swelling of the right cheek for 2½ months Physical examination revealed moderate fullness and hypesthesia over the right cheek The initial laboratory studies and chest film were negative Skull films revealed thickening of the right zygoma and anterior wall of the right antrum X-rays of the pelvis revealed an osteoblastic reaction involving the right ischium and acetabulum highly suggestive of Paget's disease

A Caldwell Luc operation was performed April 18 and a large cystic mass overlying the entire right maxillary sinus removed The microscopic diagnosis was lymphosarcoma, large cell type

Despite adequate irradiation to the right maxillary region and subsequent therapy directed at pulmonary metastases, the patient expired July 9

Autopsy revealed extension of the original tumor through the anterior medial wall of the middle cranial fossa and lateral wall of the right orbit into the retrobulbar fat In addition to involvement of the lungs, liver, stomach, small bowel, adrenals, kidneys and lymph nodes, there was massive replacement by tumor of both testes and epididymides Microscopic examination of the testes revealed a diffuse infiltration by neoplastic cells of the lymphocyte series between the seminiferous tubules (fig 1)

Case 2 J H , a 62 year old white man, entered the hospital January 8, 1952 with a swollen left scrotum and testis of 4 to 5 weeks' duration Past history

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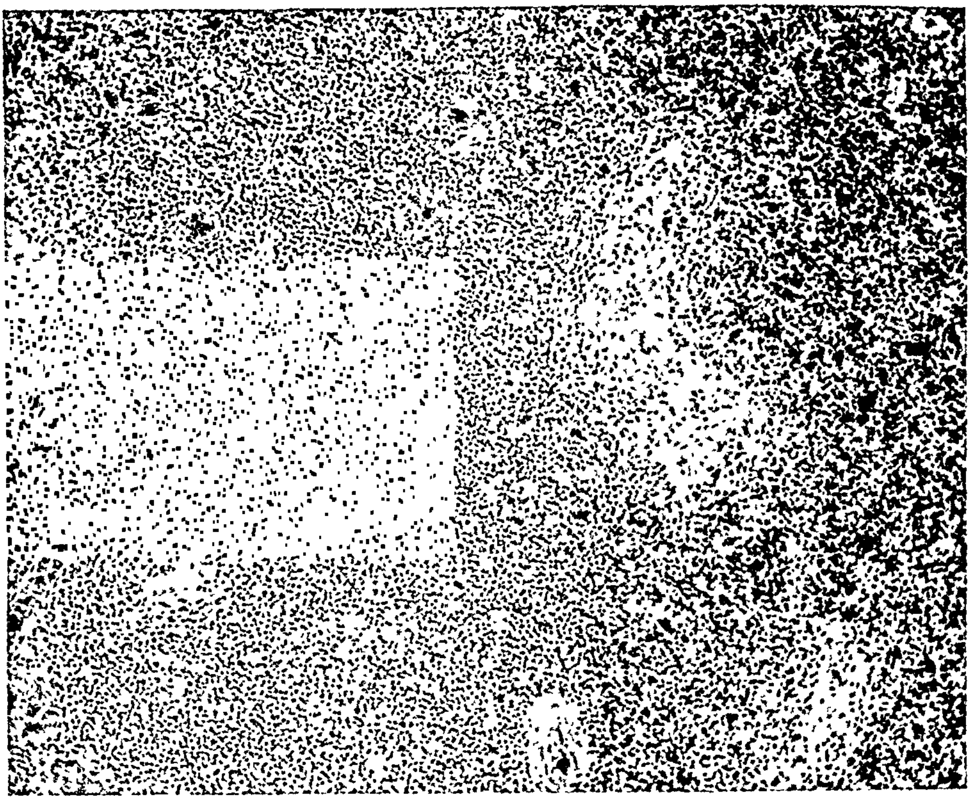

FIG. 1. Case 1. Note dense replacement of normal testicular parenchyma by lymphoblasts. ×100.

revealed a right orchiectomy in November 1950 followed by 32 deep x-ray treatments to the right scrotum and inguinal region.

The admission laboratory studies, Friedman test and chest film were negative. Cystoscopy and retrograde pyelograms were nonrevealing.

Because of the past history of a right testicular neoplasm, a biopsy of the left testis was performed January 10 and revealed lymphosarcoma, small cell type. In order to determine the radiosensitivity of the tumor a total dose of 2,400 r. (skin dose) was directed to the left testis over a 5-day period, and left orchiectomy was performed February 12. Microscopic examination revealed only fibrosis and atrophy with no evidence of tumor involving the testis; however there was neoplastic invasion of the spermatic cord by lymphosarcoma, small cell type (fig. 2). Irradiation therapy to the right and left inguinal regions, epigastrium, umbilical area and inferior and superior lumbar fields was then resumed, a total of 4,000 r. (skin dose) being given. Despite this cancerocidal bombardment cutaneous metastases developed and the patient expired May 24 in uremia. Autopsy revealed massive involvement of the heart, lungs, liver, pancreas, kidneys, adrenal glands, subcutaneous tissues and lymph nodes by lymphosarcoma, small cell type.

Of incidental interest is the fact that slides of the previously removed right testicular tumor revealed embryonal cell carcinoma. The patient, although the

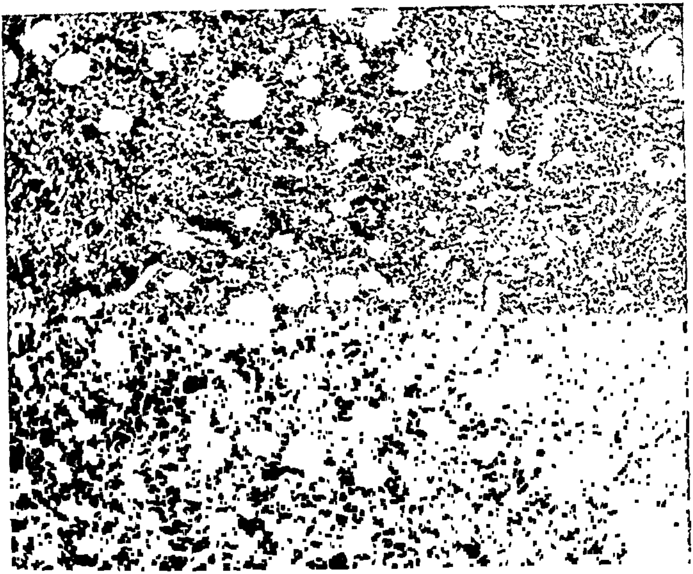

FIG. 2. Case 2. Lymphosarcoma of spermatic cord missed by cancercidal irradiation directed at testis. ×100.

unfortunate victim of two deadly tumors, apparently survived the first cancer as no traces of it were discovered at autopsy.

Case 3. M. Z., a 58-year-old white man, entered the hospital on August 16, 1952 with a 3 months' history of a left scrotal mass. Examination revealed a markedly firm, nodular mass involving the left testis and epididymis.

All laboratory studies, including a Friedman test, were negative. Chest film and skeletal survey showed no metastases.

On August 22 a left orchiectomy through an inguinal approach was performed. The pathological diagnosis was lymphosarcoma, large cell type (fig. 3).

The patient was started on irradiation therapy 1 week following operation and received approximately 2,500 r. (skin dose) to the left inguinal, umbilical and epigastric fields anteriorly and the lumbosacral, lumbodorsal fields posteriorly. He was discharged asymptomatic on October 10 with no evidence of metastases. He re-entered the hospital on June 11, 1953 because of radiographic evidence of several ill defined nodules in the right lower lung field, first evident on a chest film taken on April 23, 1953. Irradiation therapy was given to the anterior and posterior right lung fields, total dosage consisting of 2,400 r. (skin dose), with complete disappearance of the nodular densities. Readmission on September 21, 1953 was necessary because of metastatic nodules in the left lung field. These completely resolved following 1,800 r (skin dose) to the left hilum and anterior and posterior left lung fields.

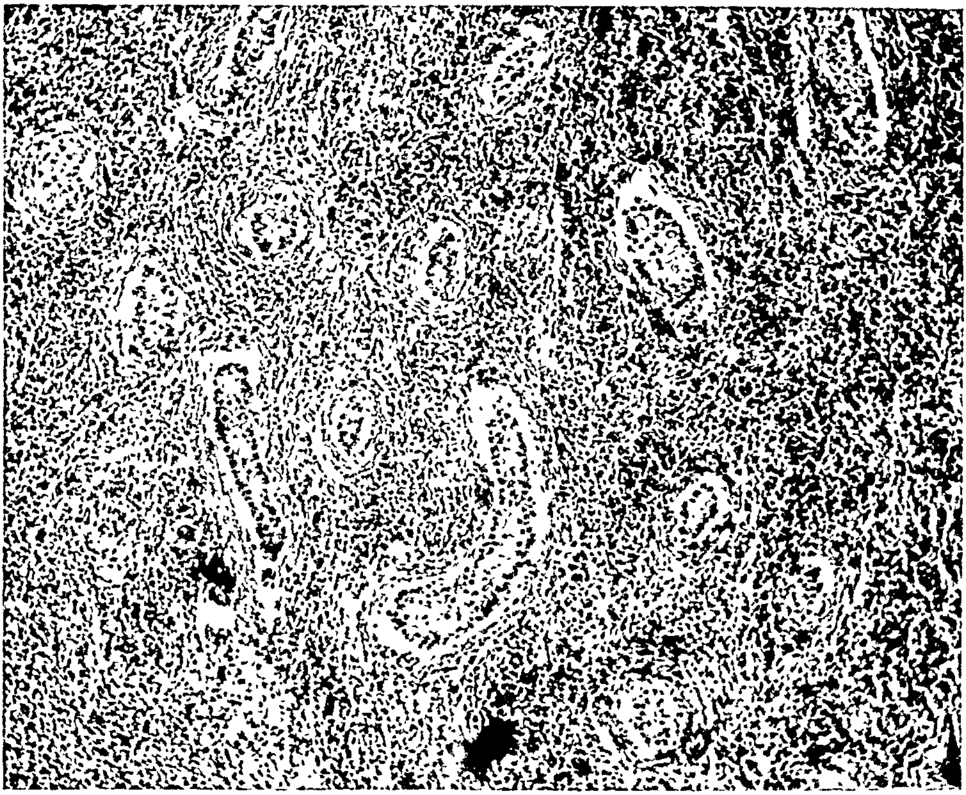

Fig. 3. Case 3. Note dense infiltration by anaplastic cells with compression of seminiferous tubules. ×100.

At the present date the patient is free of demonstrable metastases based upon excretory pyelography, skeletal survey and repeated chest films.

Case 4. P. K., a 66-year-old white man, entered the hospital on August 12, 1953 complaining of bilateral scrotal enlargement of 2 years' duration. Physical examination revealed an enlarged, firm, right, anterior, cervical lymph node. The right scrotum was occupied by a firm, nontender mass, measuring 20 by 10 cm. The left scrotal cord was indurated and fixed.

The admission chest film (fig. 4, *A*) revealed a confluent and linear increase in density throughout the right lower lung field. There were several large nodular densities in the posterior right lung and an osteolytic lesion was noted involving the posterior portion of the right eighth rib. An excretory urogram showed no excretion of contrast medium on the left side. Otherwise the laboratory studies were negative.

In view of the cervical adenopathy and the bilaterality of the testicular masses, the clinical impression was lymphoma and bilateral orchiectomy was performed on August 14, 1953 in order to establish a working diagnosis (fig. 4, *B*). The microscopic examination revealed lymphosarcoma, small cell type (fig. 5).

Despite intensive irradiation therapy this patient maintained a febrile course and expired on September 30, 1953.

Autopsy revealed widespread lymphosarcoma of the small cell type involving the lungs, lymph nodes, liver, pancreas, adrenals, thyroid and left kidney with obstruction of the left ureter by enlarged retroperitoneal lymph nodes.

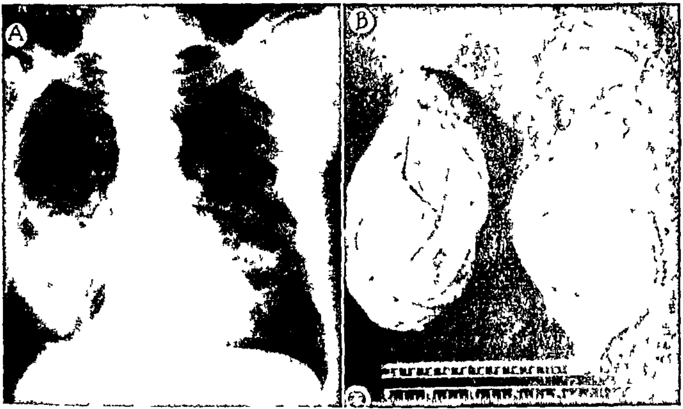

Fig 4 Case 4 *A*, note metastatic focus in right lung suggestive of abscess *B*, gross specimen exhibiting unusual involvement of adventitial tissues by tumor

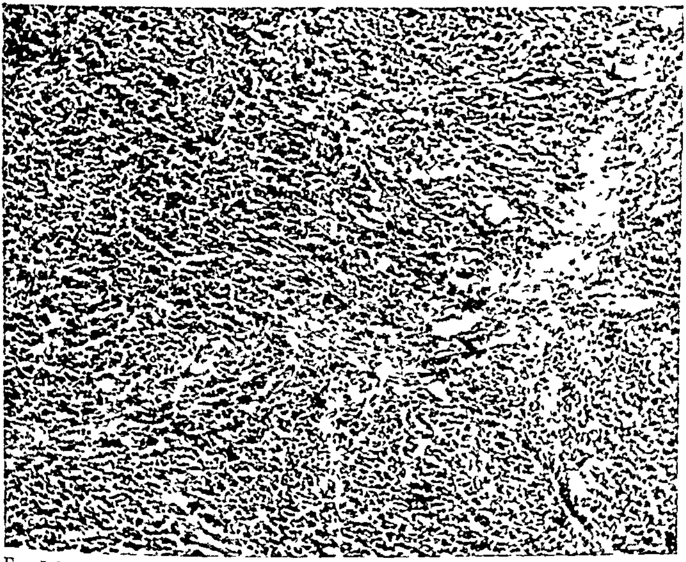

Fig 5 Photomicrograph demonstrates complete obliteration of normal testicular architecture ×100

Case 5 C G, a 38 year old white man, was admitted on July 29, 1953 with a 7 months' history of persistent nasal discharge Physical examination revealed a markedly swollen nose with the right naris obstructed by a necrotic tumor mass There were several slightly enlarged, firm, nontender lymph nodes in the right anterior cervical chain. The admission hemogram, urinalysis and serology were within normal limits. The admission chest film and three subsequent films were negative.

A biopsy of the right intranasal lesion shortly following admission was interpreted as lymphoepithelioma. The patient was given 7,100 r. through three portals to the nasal region with apparent good results. On August 22, 1935 an arciform, erythematous nodule appeared on the left thigh. Biopsy revealed only chronic inflammation, and the lesion disappeared following 1,000 r. of irradiation. Despite the uniform response of the initial lesions to irradiation, new skin lesions appeared and the original nasal tumor recurred. The patient expired on February 9, 1936. At autopsy, massive involvement by tumor of the lungs, lymph nodes and skin was observed. In addition, a well circumscribed, firm yellowish-gray nodule, 2.5 cm. in diameter was discovered in the left testis. The diagnosis was lymphosarcoma, large cell type. The microscopic picture revealed many lymphocyte-like cells infiltrating the interstitial tissues of the testis. The tubules exhibited varying degrees of degeneration.

DISCUSSION

Lymphosarcoma is classified as one of the lymphoblastomas. In this group of neoplasms are also included reticulum cell sarcoma, lymphoid leukemia and Hodgkin's sarcoma. The disease occurs occasionally in the younger age group, but affects predominantly those in the fifth and sixth decades. Males are afflicted three times more frequently than females. The youngest reported case of testicular lymphosarcoma was a 4-year-old Negro boy. The average age in this series of 5 patients was 56.4 years.

The lymphoblastomas are the most common cause of bilateral testicular tumor and accounted for 50 per cent of 21 cases reported by Hotchkiss and Laury. Case 4 of our series presented this picture, and cognizance of this fact aided in the clinical diagnosis of lymphoma. It should be stated that bilateral primary testicular carcinoma is extremely rare.

Most authorities agree that the testicular involvement is only part of a diffuse metastatic infiltration of multiple organs. However, Mathé in 1946, Gandin and Konwaler in 1951, and Turley and Moore in 1952 reported cases in which the testicular tumor was the presenting abnormality and very possibly represented the primary site of the disease. The findings in two of our cases would appear to support this thesis. Case 2 exhibited a primary testicular mass that was the only evidence of disease until cutaneous metastases appeared 3 months later. Case 3 progressed 11 months following initial diagnosis and orchiectomy before pulmonary metastases were noted; the patient is now living and well 2 years after orchiectomy and irradiation therapy without evidence of generalized disease. Hutchinson's case, reported in 1889, died from widespread metastases 3 years following orchiectomy.

The paradox of how a lymphoma may arise in an organ that does not contain lymphoid tissue has given rise to several interesting theories regarding etiology. Ficari cites the prostate (15 reported cases) and the urinary bladder (6 reported cases) as nonlymphoid organs presenting primary lymphosarcoma and postulates that the neoplasm may either originate from residual postinflammatory lymphoid tissue or may represent specific differentiation of a pre existing teratocarcinoma This interesting controversy of primary origin versus secondary invasion poses an academic desideratum Should lymphosarcoma, originally manifest and only demonstrable as testicular tumor, be added to the classification of primary malignant testicular tumors, or should the occasional testicular involvement be considered as part of a widely disseminated process? Prudence would seem to demand that final judgment be withheld until more statistics and studies have been compiled

It is interesting to note that the nasopharynx, richly endowed with lymphoid tissue, appears to be the most common primary site of lymphosarcoma, with eventual spread to the testis, having been demonstrated in over 20 per cent of the reported cases and being the original focus in two of our cases, an incidence of 40 per cent.

The concomitant existence or subsequent appearance of cutaneous lesions is frequent and offers a definite aid in diagnosis The only other such combination under similar circumstances occurs in chorioepithelioma of the testis Cutaneous nodules were present in three, or 60 per cent, of our cases

The presence of lymphadenopathy, usually cervical or inguinal, has been noted in 40 per cent of the reported cases Splenomegaly is often detectable, but it may be absent None of our cases showed leukemic involvement

Grossly, these tumors are almost invariably confined within the tunica albuginea However they may occasionally invade the epididymis and spermatic cord Microscopically, the testicular parenchyma is massively infiltrated or replaced by a rather homogeneous sheet of cells of the lymphocyte or lymphoblast type, with only a few degenerating tubules discernible The subclassification consists of small cell or large cell lymphosarcoma, utilizing the most predominant cellular pattern as a basis for diagnosis Reticulum cell sarcoma may be confused with the above, but it can be differentiated by use of a reticulum cell stain Hodgkin's sarcoma and lymphatic leukemia occasionally infiltrate the testis, but they seldom give rise to gross enlargement and there is invariably sufficient clinical and microscopic evidence present for establishment of their distinctive identity

The usual treatment of lymphosarcoma of the testis has been orchiectomy followed by irradiation therapy However, 2 cases treated with nitrogen mustard have been reported One patient so treated by Hotchkiss and Laury was unaffected, but Gandin and Konwaler's patient showed some initial improvement following 28 gm of the agent

The prognosis is poor, with survival varying from 6 months to 3 years following onset of symptoms and/or signs

CONCLUSIONS

Lymphosarcoma of the testis is a rare disease usually secondary to a primary origin elsewhere in the lymphoid tissues of the body It may, however, present itself as a primary tumor of the testis and must therefore be considered in the differential diagnosis of testicular tumor. The diagnostic probability of its existence is enhanced by the presence of bilateral testicular tumor with the concomitant presence of skin lesions and lymphadenopathy.

Although the lesion responds to irradiation therapy, the eventual prognosis is poor.

The author expresses his appreciation to Dr. Thomas Kinney of Cleveland City Hospital for permission to use case 5.

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TREATMENT OF INOPERABLE PROSTATIC CARCINOMA BY Au_{198}

LOUIS M. ORR, JAMES L. CAMPBELL AND MILES W. THOMLEY

Cancer of the prostate is considered the most common malignancy in men after 60 and probably occurs in 20 per cent of all men past that age. In routine autopsy studies 6 pathologists found small latent foci of prostatic carcinomas in 14 to 46 per cent of men over the age of 50. Ten per cent of routine benign prostatic specimens, when rechecked and intensively examined, were also found to be malignant. With the increase in life expectany all of us have become more respecful of this malignancy of the aged, since its frequency, no doubt, will increase with longevity.

The cause of cancer of the prostate is unknown although it would certainly appear to be the result of some chemical or hormonal imbalance. It is generally agreed that 90 per cent of prostatic carcinomas originate in the posterior lobe. The lesion is slow growing and usually metastasizes late. For this reason carcinoma of the prostate is asymptomatic until extension beyond the confines of the capsule, or distant spread, has occurred.

The imperativeness of rectal examination cannot be overemphasized since digital palpation is the most valuable single diagnostic factor in detecting early cancer of the prostate. It has been estimated that one can accurately diagnose benign prostatic hypertrophy in 96 per cent of all cases and carcinoma in 88 per cent by rectal examination.

It is generally agreed that early prostatic carcinoma should be treated by radical prostatectomy. Patients between 75 and 80 years of age, whose life expectancy is only a few years, possibly should not be subjected to radical prostatectomy for they do not tolerate the procedure well at this age. It has been estimated that only 5 to 10 per cent of prostatic carcinomas are diagnosed sufficiently early to be cured by radical surgery. This small percentage is the result of 1) the failure of early prostatic carcinoma to produce symptoms, 2) the failure of the examiner to perform periodic rectal examinations, and 3) the failure of male patients to voluntarily seek periodic rectal examinations.

Over one hundred and fifty years ago John Hunter observed that castration produced atrophy of the normal prostate gland and in the latter part of the nineteenth century White reported that castration was of benefit in 85 per cent of the patients with obstructive prostatism. However, it has been only in the past 15 years that endocrine therapy of the prostatic cancer has been introduced and developed.

The first reports of estrogenic management of prostatic carcinoma were made by Huggins[1] and others in 1941. At about this time Munger[2] used external radia-

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Read at annual meeting, Southeastern Section of American Urological Association, Palm Beach, Fla April 12–15, 1954.

A detailed account is available in T [illegible] -131.

[1] Huggins, C , Scott, W. W. and H [illegible] ts of fever, of desoxycorticosterone and o [illegible] carcinoma of prostate. J. Urol., 46: 997–1006, 1941.

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tion to decrease the androgen factors in the treatment of prostatic malignancy. In 1945 Herbst and Sauer[3] introduced radiation of the pituitary and Huggins and Scott[4] observed the effect on prostatic carcinoma by removing the adrenal and pituitary glands.

One of the most important factors to consider in inoperable carcinoma of the prostate is the patient's age. Certainly life expectancy is greater today than ever before and as a result we are seeing more men with advanced cancer of the prostate. Insurance charts show that life expectancy for a 75 year old man is 6 years. Since the life span has been increased we are striving to afford the increasing number of patients afflicted with prostatic malignancy longer and more comfortable survival periods.

Actually, however, the survival time has been increased very slightly. Nesbit and Plumb[5] in 1946 revealed that in 795 untreated prostatic carcinomas the average survival from time of diagnosis was 21.2 months. A series of 485 cases presented by Bumpus[6] revealed a survival time of 31 months. These cases were also untreated by estrogenic therapy. Survival at the present time, by utilization of all forms of palliative therapy, has increased only an additional 9 to 18 months.[7] This makes us wonder whether this is a real or an apparent increase in survival time, since it would appear logical to assume that we are, undoubtedly, seeing prostatic carcinomas earlier today than a few years ago. It is entirely possible that the increase in survival time may be in direct proportion to the increased interest in geriatrics and improvement in general care of the aged.

To realize that estrogenic therapy, despite its widely heralded virtues, has really contributed so little to the increase in survival time of the patient with inoperable cancer of the prostate, is, to say the least, most surprising and, at the same time, disappointing. It is no doubt a realization of these facts that prompted Flocks[8] in 1951 to first instill a radioactive isotope, Au_{198}, into the prostate gland of patients with hopeless carcinoma of that organ. Since his original report Flocks has now reported on more than 200 patients treated by this method. His results have been sufficiently encouraging to stimulate other investigators along the same lines of endeavor.

It was determined years ago that irradiation with the roentgen ray or radium was ineffective in the treatment of cancer of the prostate. The question which immediately arises is why would the use of a radioisotope be more effective than roentgen therapy or radium.

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Isotopes have several unique properties not possessed by x-ray, radium, radon, or even cobalt as presently employed. Most important of these is that an isotope is a form of radiation suspended in a solution as a stable colloid containing millions of small particles. These small particles represent multiple point sources of radiation which are separated by varying distances.

Au_{198} was selected as the most suitable isotope for use in prostatic cancer because of its stability, its favorable half-life of 2.7 days, its relative uniformity in arrangement of its molecular pattern, its proportion of gamma and beta radiation and its relatively low cost of production.

PROBLEM OF DOSAGE

In the use of any radioactive isotope, which is injected interstitially for the treatment of cancer, the problem is not simply one of how many millicuries to use but rather how the radioactive material is distributed throughout the tumor and how long it remains at the site of the injection.

The cancerocidal dose in terms of roentgens delivered to the tumor has been fairly well determined in the case of most tumors by years of treatment with radium and x-ray and it has been shown that optimal results are obtained by using a dose which falls within fairly narrow limits. *Under*dosage results in a therapeutic failure whereas *over*dosage may actually decrease rather than increase the cure rate and produce many undesirable sequelae and complications. Although this dosage can be rather simply determined with x-ray, the problem is much more complex in the case of interstitially injected radioactive isotopes. The dosage received from beta and gamma radiation is easy to calculate if it is assumed that there is an absolutely uniform distribution of the isotopes throughout the tumor, provided that the exact size and volume of the tumor are known. Unfortunately, these ideal conditions never occur in actual use. The problem then, actually, is trying to determine the varying doses in different parts of the injected tissue since it is not the average dose we are interested in but rather the maximum and the minimum doses.

In the use of radioactive gold interstitially, the problem of radiation dosage is that of gamma and not beta dosage. At first glance, this statement seems rather surprising in view of the fact that the beta radiation is roughly ten times greater than the gamma rays, if one assumed an equal distribution throughout the tissues. Since gold does not have a homogeneous distribution the radiation must be computed from multiple point sources of radiation which are separated by varying distances. The beta particles of radioactive gold have an effective range of only one millimeter and any tumor cells which were not within one millimeter of the radioactive gold would be unaffected by this radiation. The effect would be that while some of the cells would be intensely irradiated by beta particles, other tumor cells would receive no radiation whatsoever. With gamma radiation the dosage also drops off fairly rapidly from a point source due to the inverse square law. With multiple point sources there is cross firing of tumor cells from many different points of radiation with the result that all of the tissue is irradiated although there may be a difference of more than one hundred per cent between the minimum and maximum dose, assuming that the point sources are not separated by a distance of more than five millimeters. If the distance between the point sources is greater than five millimeters, the difference between the minimum and maximum dose will be much greater and a point is finally reached where portions of the tumor are receiving less than a cancerocidal dose.

In order to diminish the difference between the minimum and maximum dose, it is necessary to produce as uniform a distribution of the isotope as possible in the injected tissues. Having determined the most desirable volume, how many millicuries should be used in order that the minimum dose will approach the known cancerocidal dose and the maximum dose will not be large enough to produce undesirable sequelae?

The importance of knowing these factors must be self evident since the results to be obtained in treating patients with carcinoma of the prostate will depend to a large extent on how carefully the radiation is administered. These factors can be determined experimentally although this has not been done up to the present time. By obtaining injected material from both man and animal, it would be possible by radioautograph to determine the distribution of the gold and the variation in dosage received by different portions of the prostate could be determined by making multiple radio assays of different portions of the prostate.

INDICATIONS AND CONTRAINDICATIONS FOR USE OF Au_{198}

The best chance of cure of cancer of the prostate, which is confined within the capsule of the gland, is total prostatectomy including removal of the seminal vesicles. The use of radioactive isotopes in such a condition is definitely contraindicated. Evidence of spread of the cancer beyond the area of the prostate and its immediate contiguous structures, as determined by marked elevation of the serum acid phosphatase physical examination, or bony metastases, precludes the usefulness of interstitial radiation with an isotope. The general condition of the patient and any serious complicating illnesses must also be considered before using this type of therapy.

DISCUSSION OF CASES

Our results in the treatment of 26 consecutive cases of advanced carcinoma of the prostate with Au_{198} have been for the most part very encouraging (table 1). The earliest cases of any series are as a rule subject to the greatest complications and the poorest results. Conversely, as the technique is improved and selection of cases is better, the end result becomes more gratifying. We have had a total of 4 deaths and these occurred in the first 6 cases (table 2). Likewise, almost all the serious complications arose in the first 10 patients treated (table 3). In cases presently treated serious complications are practically nonexistent.

In describing the local changes that take place in many extensive, large, stony-hard prostates, one must exercise restraint for fear of being too enthusiastic. However, as a rule, the entire area undergoes a softening and shrinking process that results in a flat or even concave prostatic bed. Many of these have already had the benefit of previous estrogenic therapy and have either failed to respond to it or the carcinoma has been reactivated. Not only has an atrophy of a large

TABLE 1

Case No	Age	Serum Acid Phosphatase	Size of Prostate	Dosage of Au^{198}	Results
1	56	4 0	++	40 RP* 10 Pr†	Fair
2	52	3 1	+	8 RP 5 Pr	Expired
3	73	5 3	++++	112 5 RP 20 Pr	Expired
4	65	6 5	++	40 RP None	Expired
5	81	3 7	+	75 RP None	Good
6	75	6 0	++++	145 RP None	Expired
7	80	3 0	+	15 RP None	Excellent
8	67	1 1	+++	55 RP None	Excellent
9	67	1 5	+++	100 RP None	Expired
10	66	2 2	++	75 RP None	Excellent
11	78	6 5	+++	75 RP None	Fair
12	75	2 3	+++	85 RP None	Fair
13	65	3 0	+++	70 RP 10 Pr	Good
14	76	1 0	++	90 RP 10 Pr	Excellent
15	67	2 0	+++	85 RP 20 Pr 95 Pr§	Poor
16	58	3 0	+++	90 RP 10 Pr	Excellent
17	74	2 0	+++	80 RP 10 Pr	Excellent
18	75	1 5	+++	100 RP 10 Pr	Excellent
19	55	1 6	+++	95 RP 20 Pr	Excellent
20	75	2 5	++	112 RP None	Excellent
21	69	2 2	+++	100 RP 15 Pr	Poor
22	68	3 4	++	108 RP 20 Pr	Excellent
23	68	1 2	None‡	80 RP 15 Pr	Excellent

TABLE 1—*Continued*

Case No	Age	Serum Acid Phosphatase	Size of Prostate	Dosage of Au_{198}	Results
24	58	4.1	++	95 RP 20 Pr	Excellent
25	70	1.8	+++	85 RP 20 Pr	Excellent
26	67	3.6	+++	105 RP 20 Pr	Excellent

* Retropubic.
† Perineum.
‡ Previous prostatoseminovesiculectomy.
§ Second admission—open perineal instillation.

TABLE 2. *Analysis of deaths*

Case Number	Age	Remarks
2	52	Died 3rd P.O. day—massive pulmonary embolus
3	73	Died 4th P.O. day—extensive metastasis to bone and soft tissues
4	65	Died 6 months P.O. of generalized carcinomatosis
6	75	Died 2nd P.O. day—extensive metastasis to liver
9	67	Died 5 months P.O of extensive metastasis

TABLE 3 *Complications*

Total patients involved	8
Pulmonary emboli (one recovered)	2
Delayed wound healing	5
Rectal irritation with hemorrhage	2
Postoperative bladder calculi	2
Severe postoperative nausea	2
Urethral stricture.	1

percentage of viable tumor tissue taken place, but the chance of early metastasis has been minimized by the pick up of the beta particles in the lymph vessels draining the area.

The average age of the patients in our series was 68.8 years with the youngest being 52 and the oldest 81. Estimates of the size of each prostate were attempted preoperatively and average of these estimations was 32 gm. The dosage of Au_{198} delivered into each gland was generally based on its size and the amount of tumor present. The average dose given per operation was 90.3 millicuries. In view of the average size this gives an average ratio of 2.1 millicuries per gram of tissue, which is higher than the reported optimum dosage. The largest dosage to any one patient was 200 millicuries, however, this was delivered in two separate operations of 5½ months interval. The largest dosage given at a single operation was 145 millicuries and the smallest 25 millicuries.

One of the many advantages of this type of therapy is the ease with which additional Au_{198} can be injected perineally as nodules or areas of hardness develop. As many as 5 to 7 cc of the colloidal gold may be injected through spinal needles through the perineum with no ill effects. This method has been employed on four occasions with good results.

COMPLICATIONS

Delayed wound healing and prolonged suprapubic drainage of urine have been the most frequent complications (table 3). All patients have remained hospitalized until drainage has stopped. The average period of hospitalization has been 22 days. The shortest period of hospitalization was 13 days. It is felt that the inflammatory reaction from radiation has a definite effect on wound healing but there is apparently little relationship between the millicuries/gram ratio and wound healing. There have been two pulmonary emboli. The first occurred 4 days' postoperatively and resulted in immediate death. The other occurred 27 days' postoperatively in a patient whose incision was slow to heal and he simply would not move or get out of bed. Recovery was uneventful in the latter case.

SUMMARY AND CONCLUSIONS

An outline is presented showing why Au_{198} is the isotope of choice at the present time in the treatment of inoperable prostatic carcinoma. The technique of instillation and a series of 26 cases have been presented with a discussion of results obtained by retropubic and perineal instillation of Au_{198}.

Other subjects of great importance which have received very little attention are: 1) Of the gold injected into the prostate, how much remains in the gland? How much is lost in the urine, through drainage at the operative site, through gold spilled and removed from the body in the operating room, and gold which goes by blood stream to the liver? 2) How much gold goes to the adjacent lymph nodes and is this sufficient to have a cancerocidal effect? Flocks,[9] in a recent personal communication, is convinced that this effect is produced by Au_{198}. 3) What is the dosage received by the rectum, adjacent to the prostate, and how can this be reduced without affecting the treatment?

These are only a few problems that arise in connection with the use of interstitial gold therapy which must be solved since by so doing we would materially improve the results by treatment as well as to eliminate, insofar as possible, undesirable radiation reactions.

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[9] Flocks, R. H : Personal communication, 1954.

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USE OF ANTIHISTAMINES AND THEIR LOCAL ANESTHETIC EFFECT

ROBERT R. BROWN

This brief report is to describe our experience with the local anesthetic action of an antihistamine drug. At least 17 articles may be found in the literature describing this property. The use in urology, for urethral anesthesia principally, was described by Fitzpatrick, Orr and Stubbard in the *J.A.M.A.*, November 15, 1952. Although the reports have been generally favorable and it is known that this group of drugs has a very low toxicity, a suitable preparation is still not available commercially. However, it may be obtained from a manufacturer for experimental use, and may be on the market this fall.

We first tried tripellennamine (pyribenzamine, Ciba), the drug used by the above mentioned authors, in January 1953.[1] This drug was obtained in crystalline form (through the courtesy of the Ciba Pharmaceutical Co.), and aqueous solutions were prepared by us and sterilized by boiling.

The aforementioned authors used a 2 per cent solution but we found that many patients complained of a burning sensation immediately following its instillation, lasting one to two minutes, and therefore, for the past 18 months, we have used the drug in a 1 per cent solution, and found that it caused less burning.

The method used to obtain local anesthesia was to instill 5 cc of the solution into the anterior urethra, retaining it with a penis clamp for about ten minutes. This method was used routinely for the passage of sounds, catheterization when examining patients for the first time or for unusually sensitive patients, and for manipulation of filiforms, bougies, and so forth. For office cystoscopies, the method was augmented, being to instill 5 cc in the urethra as before, and five minutes later instill 15 cc into the bladder through a catheter, and 5 cc more into the urethra, waiting ten more minutes before proceeding with the examination. When used for cystoscopies of patients who had no hematuria or who did not give a history of allergy to procaine preparations, the drug was supplemented by placing two one grain procaine tablets into the posterior urethra through the Bransford-Lewis urethral tablet depositor. This was done following the catheterization.

Tripellennamine in 1 per cent solution has been used approximately 500 times for urethral manipulations of various types, and 24 times for cystoscopic examination of male patients. The small number of cystoscopies has all been performed in recent months after we were satisfied as to the safety and efficacy of the drug. Follow-up records were kept for the first 100 procedures. Many of the treatments were repeated periodically on the same patient, and a good follow-up was obtained.

The results were highly favorable. There were no reactions of a systemic

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[1] This drug is now available.

nature either immediate or delayed, and no delayed local reactions. The only complaint, and that frequently elicited only by querying the patient, was of a mild burning sensation usually lasting one or two minutes. This sensation caused apprehension occasionally among the group of highly nervous patients, but it usually subsided by the time we had finished reassuring them. Only one patient complained of considerable burning and dysuria, a patient who had a Hunner ulcer. Patients who were unable to tolerate drugs of the procaine group because of allergic reactions either immediate or delayed, tolerated this drug quite well. As regards the level of anesthesia, the follow-up questioning of the patient, which, of course, is not too reliable, gave the impression that the anesthetic effect was satisfactory in 90 per cent of the treatments. This group felt that it was as effective or occasionally more effective than previously used agents. Those who had to forego anesthesia because of sensitivity are particularly grateful. The remaining 10 per cent preferred the older medicinals either because of the burning, or because they thought the anesthesia level was lower.

We have just recently received for trial a 2 per cent preparation in sterile jelly, and therefore have used it in only a few patients. There was still less burning complained of with this form, but the number of cases is too small to more than just mention its use.

In summary, we believe that tripellennamine in a 1 per cent aqueous solution has three outstanding advantages: 1) it is safe and free of reactions; 2) it can be sterilized by boiling; 3) it produces satisfactory anesthesia.

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A MODIFICATION OF THE BUNGE URETERAL MEATOME

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Bunge introduced a ureteral meatome for use in the treatment of the ureterecele and the impacted calculus in the intramural ureter.

A modification of this instrument is presented (fig. 1, *A*). It differs from Bunge's instrument in that the removal of the insulating material from the incising electrode allows a much closer approximation of the wire elements. This instrument offers an incising electrode which is of uniformly small caliber throughout its cutting length of 0.8 cm.

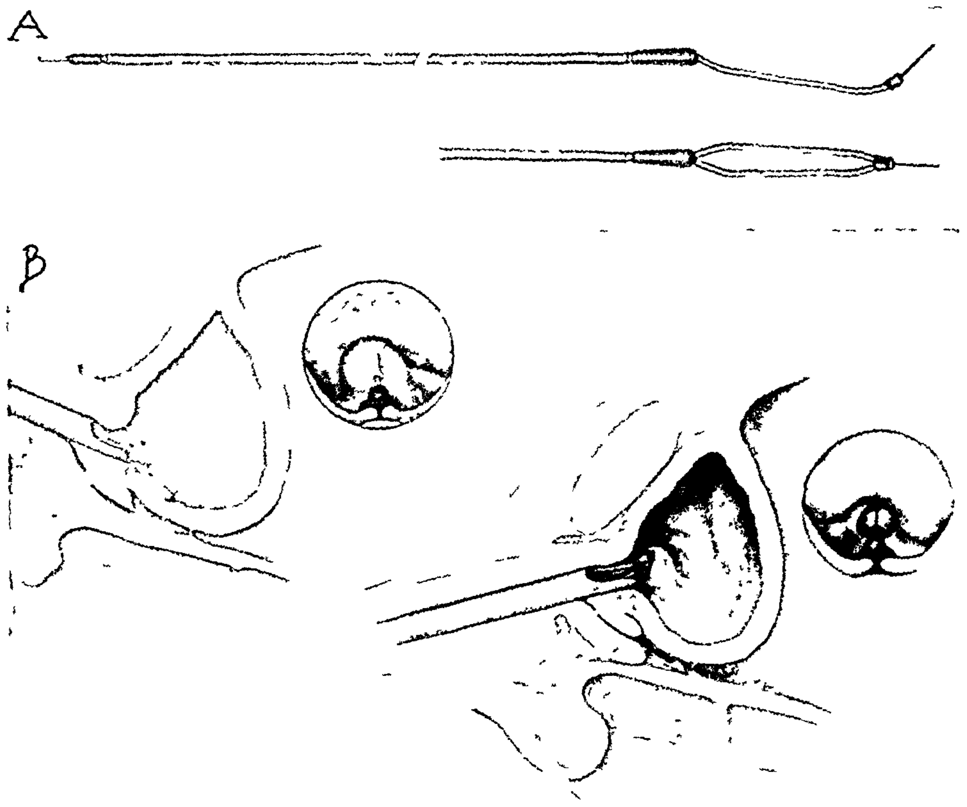

FIG. 1 *A*, author's modification of Bunge ureteral meatome. *B*, use of meatome in treatment of ureterocele and intramural ureteral calculus. Note taut, anterior ureteral wall before incision and elevation of electrode when incising.

The instrument is utilized with the resectoscope rotated 180 degrees. The cutting electrode, which easily enters the smallest ureteral orifice, is then retracted to stretch the ureteral wall superior to the orifice (fig. 1, *B*). A slight

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elevation of the distal end of the resectoscope is effected at the time the cutting current is applied. This results in a controlled, clean, sharp incision through the ureteral wall. With this technique there need be no damage to the opposing inferior ureteral wall. The rigidity of the resectoscope and the meatome insures complete control of the operative procedure.

The author wishes to express his appreciation to the Greenwald Company, Inc. of Gary, Indiana for producing this instrument.

122 S. Michigan Ave., Chicago 3, Ill.

REFERENCE

BUNGE, R. G.: A new ureteral meatome for use with the resectoscope. J. Urol., 70: 568, 1953.

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TECHNIQUE FOR RUPTURING AN NONCOLLAPSIBLE RETENTION BAG OF A FOLEY CATHETER UNDER DIRECT VISION

SIDNEY P. HURWITZ, EDWARD B. JACOBSON AND ISADORE I. KOLMAN

The Foley retention and hemostatic catheter has proven a valuable addition to the armamentarium of the urologist.

Occasionally, because of some defect in the composition or construction of the catheter, the retention bag cannot be decompressed, making it impossible to remove the catheter through the male urethra.

This complication may occur when the lumen of the catheter has become occluded, and in the presence of an overdistended bladder, removal of the catheter becomes imperative.

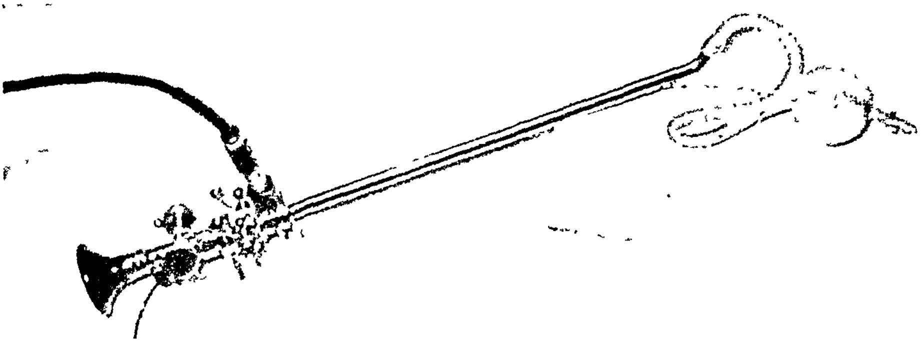

Fig. 1

When it was found impossible to collapse the retention bag by the usual methods, viz., overdistention, injection of chloroform etc., we utilized a method which permits the rupture of the bag under direct vision and the ready removal of the catheter.

The distal end of the catheter and tube to the bag is sectioned about two inches from the external urinary meatus. Its lumen is threaded on the beak of a Brown Buerger cystoscope (fig. 1), which is then passed into the bladder behind the coiled catheter. The obturator is removed, permitting the evacuation of the distended bladder contents. The catheterizing element is then introduced through the cystoscopic sheath and a ureteral catheter with the barrel of a hypodermic needle fixed in its end is passed. By directing the needle point with the deflecting lever of the catheterizing element, the retention bag is pierced under direct vision. This permits the evacuation of its contents and allows for the ready removal of the catheter, which remains attached to the beak of the cystoscope. If a Bovie unit is available, a coagulating electrode may be substituted for the needle catheter, and the bag ruptured with the coagulating current.

606 W. Wisconsin Ave., Milwaukee 3, Wis.

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PREPARATION OF AN INCONTINENCE BAG

SIDNEY P. HURWITZ, EDWARD B. JACOBSON AND ISADORE I. KOLMAN

Temporary postoperative urinary incontinence of the stress or urgency type, or a combination of the two, is not uncommon. This complication is occasionally seen after any procedure for simple prostatectomy and is more common following radical prostatectomy.

Incontinence is demoralizing at any age, particularly in the aged patient, in whom insecurity is characteristic. These patients become obsessed with a compulsive fear of being socially stigmatized for the remainder of their days. This anxiety often contributes to spasticity which increases the incontinence. They frequently brood over this condition, refuse to become ambulatory, do not take adequate food, and develop insomnia for fear of enuresis.

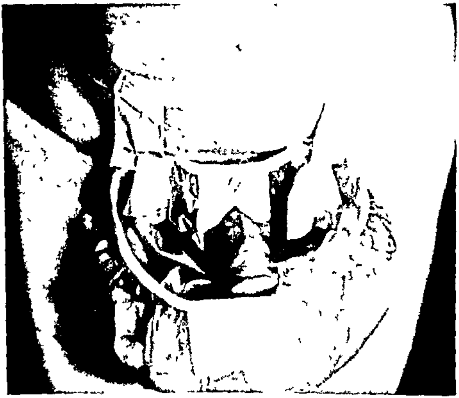

FIG. 1

The condition is distressing to the urological surgeon. He tests the bladder function, notes the patient start and stop his urinary stream at will, and correctly concludes that the prostatectomy has been well performed without anatomical damage to the sphincter. In spite of good surgery, the patient, however, remains wet. His status is comparable to the balky catsup bottle which either doesn't yield or suddenly overflows.

The patient is given a trial with medications and advised of sphincteric exercises. Upon failure to respond, he is fitted with a penis clamp, or a standard rubber urinal. Neither is comfortable and soon the genitalia become excoriated so that the apparatus is intolerable.

None of these measures take into consideration the pathological physiology and psychology involved. This complication is most often seen in the elderly

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and the arteriosclerotic patient. This suggests that cerebral arteriosclerosis plays an important role in the mechanism of this condition, in that there is impaired adaptability of the reflex of cerebral inhibition of micturition. These patients have spent years conditioning their cerebral pathways to be able to void in spite of bladder neck obstruction. They now find themselves having difficulty in the opposite direction. One might compare this to the emptying of a bottle with a small hole in its cork, as in a perfume container, when the cork itself is suddenly removed and a new adjustment is required to prevent precipitous overflow. Postoperatively, these patients require radical reconditioning of cerebral pathways with emphasis upon the reflex governing cerebral inhibition of micturition. This is a formidable task for an elderly individual.

Beyond the scope of this report are numerous accessory factors involving disuse atrophy, weakening of the internal sphincter by the surgical procedure, postoperative cystitis, either mechanical from irritation of indwelling catheter, or from bacterial infection, or combinations of the two with actual decrease in bladder capacity.

We have devised a simple type of incontinence apparatus (fig. 1) which works well for this group of patients. The method is not original; however, we have made basic modifications in construction and function. We attribute the effectiveness of this apparatus to the fact that it is directed to relieve both the underlying pathological physiology and the abnormal psychology.

The materials required are a plastic shower cap and an elastic sanitary belt. To prepare the cap, an adhesive patch is applied to the inner and outer surfaces at each angle. Another large patch is then placed midway between the first two, anteriorly and posteriorly. The posterior patch is then cut circularly of such diameter that the patient is able to insert the penis into the bag snugly.

The belt is adjusted to the patient. The penis is inserted into the hole in the bag. A safety pin is used to attach the bag to the belt at each of the original angle patches. A cellulose sponge, surgical fluffs, or sanitary napkins are placed in the bottom of the bag to absorb the urine. A deodorant may be added. The anterior and posterior edges are pinned together to contain the penis. If the patient wishes to void, he simply unpins the bag. The absorbent material is easily replaced upon saturation.

It has been rewarding to witness the results of a few minutes of mechanical effort using a few cents worth of material. This apparatus makes it possible for the patient to return to his former social environment with renewed confidence. His mental and physical status rapidly improves. He now listens with confidence to sphincteric reconditioning exercises, and within a short time discards the apparatus with complete return to continence.

In summary and conclusion, an inexpensive, readily available, easily contrived apparatus has been presented for use in temporary postprostatectomy urinary incontinence. It is not advised for total incontinence.

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SECTION MEETINGS

North Central—Chicago, Ill , September 28-October 1, 1955
Northeastern—Lake Placid Club N Y , September 22-24, 1955
South Central—San Antonio, Texas, October 17-19, 1955

Note by editor The names of new officers and members of the Executive Committee elected at the 1955 annual meeting of the American Urological Association will be printed in the July issue

A complete list of officers and members of the executive committees of the various Sections and Branch Societies will be printed in the December issue

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